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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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The Journal of Pediatrics

VOL. 36 APRIL, 1950 NO. 4

Original Communications

IMMUNOLOGIC ASPECTS OF BCG VACCINATION

A STRICTLY CONTROLLED STUDY IN INFANTS FROM TUBERCULOUS HOUSEHOLDS

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CHICAGO, ILL.

I WAS invited by the American Pediatric Society to discuss BCG vaccine. This is indeed a sign of a change in our thinking.

Before we can consider vaccination against tuberculosis, I should like first to establish the evidence of immunity in tuberculosis. There are many who still doubt that such an immunity exists. Here is some of the evidence which is unequivocal.

1. *Koch's Phenomenon.*—If a normal guinea pig is inoculated intradermally with virulent tubercle bacilli, no visible reaction can be noted for perhaps from seven to fourteen days. At that time a small nodule develops at the site of inoculation, and the draining lymph nodes become enlarged. The nodule becomes necrotic, breaks down, and ulcerates. At the same time the organisms are dispersed throughout the body of the animal and the animal finally dies of progressive tuberculosis.

On the other hand, if one inoculates the same dose intradermally into an infected animal which reacts to tuberculin, one will note in from twenty-four to forty-eight hours an intense redness, swelling, and necrosis at the site of inoculation. This necrotic area will slough out, and if smears are taken of the slough, numerous tubercle bacilli may be noted. The local lesion may go on to healing and scar formation. The draining lymph nodes will not become grossly enlarged, and culturing of these lymph nodes may be negative for tubercle bacilli; at best they would be positive only between one and three weeks after the second inoculation. (In the primarily infected animals, lymph nodes can be shown to contain tubercle bacilli a few hours after intradermal injection.[1]) In my own experiments I demonstrated that there is extension from the site of inoculation in a normal animal as early as five minutes after inoculation.[2] The organisms of reinfection are localized at the site of entrance in infected animals, whereas in the noninfected animals tubercle bacilli spread rapidly throughout the body.

From the Institution for Tuberculosis Research, University of Illinois College of Medicine, Chicago Municipal Tuberculosis Sanitorium (Tuberculosis Prevention Clinic) and Research Foundation.

Presented at the annual meeting of The American Pediatric Society at Atlantic City, N. J., May 5, 1949.

2. *Complete Protection of Animals by Immunization.*—It has been demonstrated that one tubercle bacillus will cause progressive tuberculosis in the guinea pig. If tubercle bacilli are applied to the intact or slightly scarified skin of a guinea pig, progressive tuberculosis may develop. However, if such a guinea pig is first inoculated with avirulent tubercle bacilli, and one waits until the tuberculin test becomes positive, and places virulent tubercle bacilli on the intact or slightly scarified skin, complete protection will be afforded. Likewise, small subcutaneous or intravenous injections of from .001 to .0000001 mg. of virulent tubercle bacilli will produce no demonstrable disease in such animals.[3] Most nonsuccessful experiments have employed relatively massive doses for reinfection, e.g., 0.1 or 1 mg., which would correspond to many million infective doses.

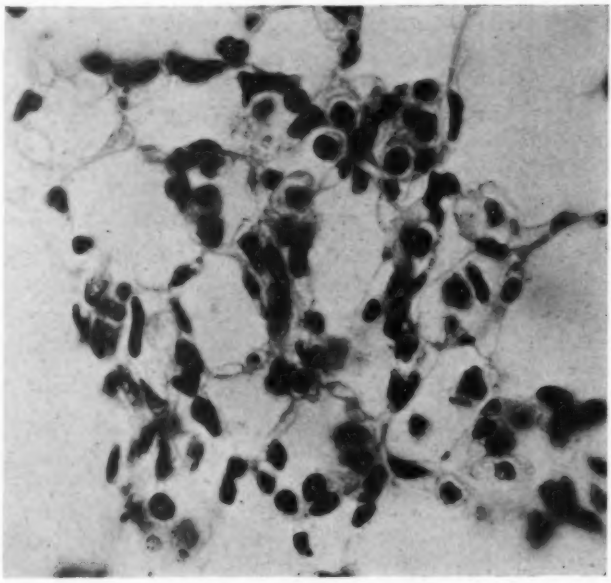

Fig. 1.—Lung, one and one-quarter hours after intravenous injection of BCG. The septal cells are swollen and arrange themselves along the inner aspect of the alveolar walls. Note the flat dark-staining nuclei of the capillary endothelium in contradistinction. (Hematoxylin and eosin ×500.)

3. *Hyperergy and Resistance to Tuberculosis in Human Beings.*—If a natural primary infection in a young adult is completely healed (as depicted by a positive tuberculin test and a negative chest film), it has been shown repeatedly that this person resists the tuberculous reinfection to a much higher degree than one who has not had the primary infection. This has been shown in one of our own studies of various institutions in the United States[4] and has been enlarged upon by Marc Daniels in a survey of some twenty reports from many parts of the world.[5] He found that in more than 8,000 student nurses who were initially tuberculin positive, 173 or 2.1 per cent of them developed tu-

berculosis in contrast to 5.8 per cent of 4,832 nurses whose tuberculin reactions were initially negative. His own survey in England of more than 2,500 nurses was 2 per cent versus 6 per cent. In contrast, positive tubercuiln reactions in infants and children more frequently indicate active infection, which may or may not progress. The interpretation of a positive tuberculin reaction differs sharply with age.

4. *The Reticulo-Endothelial System and Immunity in Tuberculosis.*—The nature of immunity to tuberculosis is not entirely understood. It is generally agreed that it is not humoral, but rather connected with the cellular responses, particularly those of the recticulo-endothelial system. I have shown[2] that the introduction into the guinea pig of avirulent tubercle bacilli, whether by the parenteral or, to a lesser extent, by the enteral route, is followed by a swelling and proliferation of the reticulo-endothelial system, especially in the lung (Figs. 1, 2, 3, and 4). This phenomenon is manifest shortly after inoculation, pro-

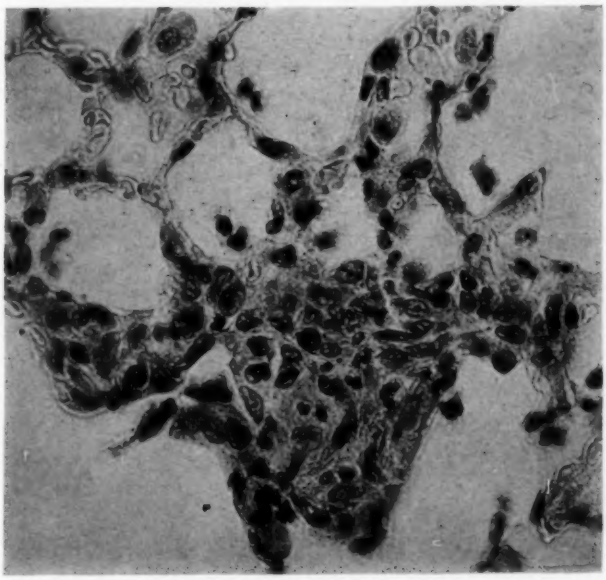

Fig. 2.—Lung, forty-eight hours after intravenous injection of BCG. A tubercle composed of a central granulocyte and intracellular tubercle bacilli and a preponderance of epithelioid cells in the periphery. (Hematoxylin and eosin ×500.)

gresses rapidly for a week or two, and then gradually recedes. The injection of large doses of tuberculin (10 mg. intracutaneously) produces a severe local reaction. The reticulo-endothelial system, especially of the lung, will swell, and a marked hyperemia accompanies the swelling (Fig. 5). The blood monocyte response trails the tissue reaction. The m/l (monocyte/lymphocyte) ratio is increased early and during the production of the local Koch's phenomenon (Fig. 6).

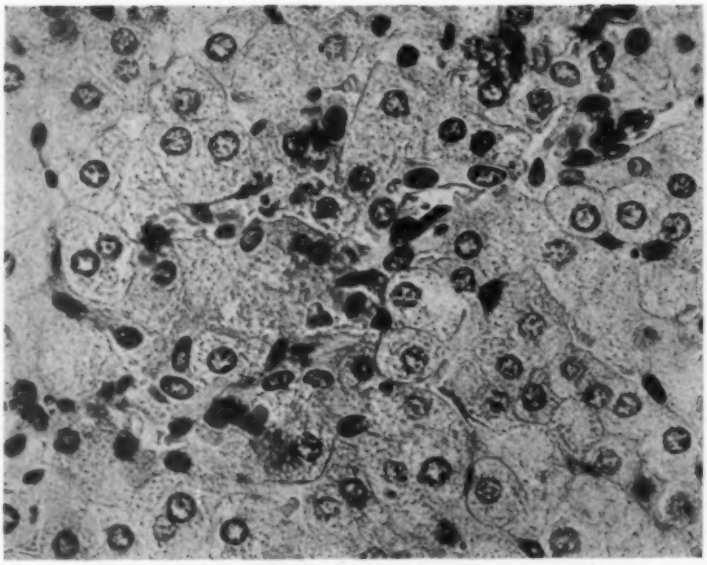

Fig. 3.—Liver, sixteen hours after intravenous injection of BCG. Note proliferation of the Kupffer cells and the grouping of same into small nodules. Some of the cells contained tubercle bacilli. (Hematoxylin and eosin ×500.)

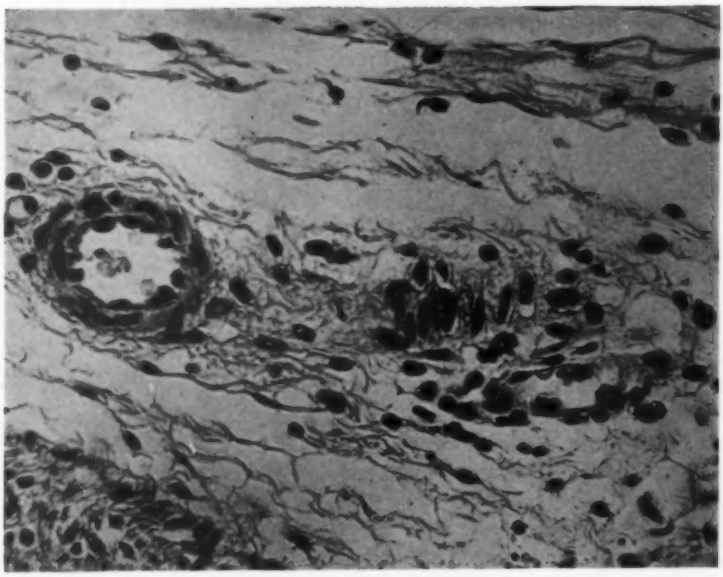

Fig. 4.—Kidney, one and one-quarter hours after intravenous injection of BCG. Peripelvic fat showing marked perivascular histiocytic mobilization and proliferation. (Hematoxylin and eosin ×500.)

HISTORY OF DEVELOPMENT OF BCG

Theobald Smith[6] was one of the first to show that the bovine tubercle bacillus differs from the human type bacillus. Human tubercle bacilli are less virulent for cattle than for humans, and, conversely, bovine tubercle bacilli are less virulent for humans than for cattle. Working on this principle, Von Behring[7] used human tubercle bacilli, which he attenuated by culturing and aging, to vaccinate calves. The results were most encouraging in that tuberculosis was prevented, but it was soon discovered that vaccinated cows would excrete human tubercle bacilli in their milk, and the vaccinations were abruptly stopped.

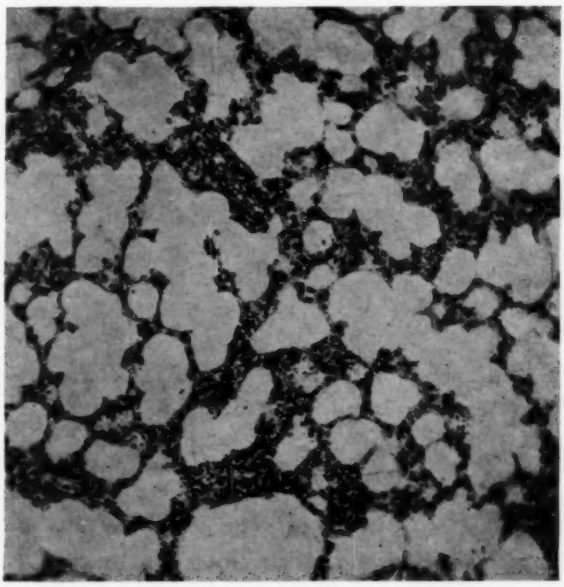

Fig. 5.—Lung, three months after intravenous injection of BCG. Moderate hyperemia and septal cell swelling following a Koch's phenomenon due to old tuberculin. (Hematoxylin and eosin ×125.)

At the same time Calmette and Guérin, who were then at Lille, began working with the idea that bovine tubercle bacilli might be used to immunize humans. Their work began in 1908,[8] using an organism which was already in the laboratory and had originally been isolated from the milk of a tuberculous cow. They began to attenuate this organism by growing it on ox bile potato media, which they showed reduced the virulence of tubercle bacilli. After five years of such cultivation it was noted that this organism, which had originally been capable of producing progressive tuberculosis in laboratory animals, now failed to do so. When it was noted after many more years that this property of avirulence was constant, immunization of animals was

begun, first in small laboratory animals,[9] then in cattle,[10] and finally in monkeys and apes.[11] Some of the early classical experiments were done as follows:

Guérin was a veterinarian, and since the problem of bovine tuberculosis was always acute in France, Calmette and Guérin concentrated their earlier work on cattle. They placed five adult tuberculous cows in one row of stalls, and in the next row behind them ten calves. Six of the calves received 20 mg. of the attenuated organism intravenously, and the other four served as controls. The vaccinated and control calves were placed alternately. The tuberculous cows were moved every week so that contamination would be uniform. After eighteen months of the experiment, none of the six vaccinated

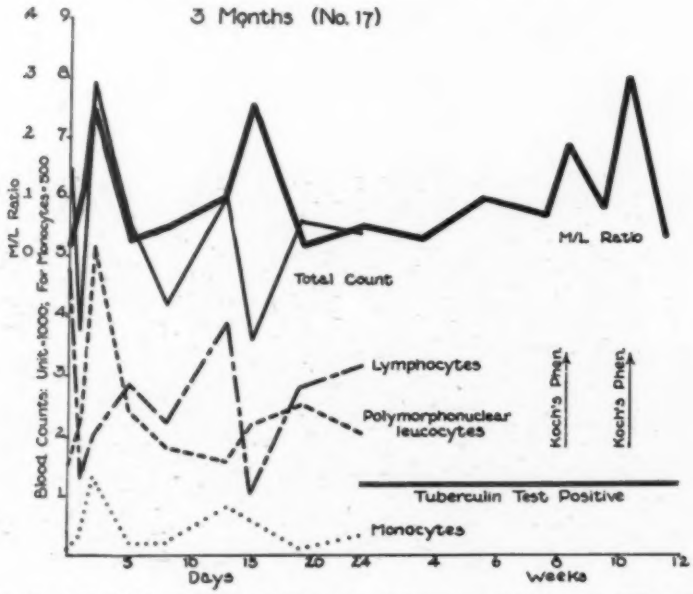

Fig. 6.—The blood response following the intravenous injection of BCG. The total monocytes in the blood increased following the mobilization of the tissue histiocytes. The m/l ratio (monocyte/lymphocyte) increased during Koch's phenomenon produced by old tuberculin.

cows reacted to tuberculin, whereas three of the four controls were infected. After thirty-two months, autopsy of all the animals revealed that three of the four controls presented extensive tuberculous lesions in the lungs and lymph nodes, only one of the vaccinated showed a small lesion in the lung and lymph nodes, while the others showed no lesions whatsoever.

A similar experiment was done on monkeys. Unfortunately, the experiments were only partly successful since so many of the animals were tuberculous when they arrived in Europe. The project was moved to French Guinea, the natural habitat of the monkeys, and the same type of experiment was done. Tuberculous animals, vaccinated animals, and nonvaccinated animals were

housed in the same cage. Practically all of the control monkeys and chimpanzees died of tuberculosis, whereas none of the vaccinated animals showed signs of the disease.[11]

After numerous similar experiments it was definitely established that the attenuated organism did not produce progressive disease in animals, and that it would protect against natural infection by virulent tubercle bacilli. Such was the beginning of the bacillus Calmette and Guérin (BCG).

THE BACILLUS

Now that I have discussed some of the immunological properties of the organism, I wish to discuss some of the properties of the bacillus itself. It behaves much the same as a bovine tubercle bacillus on culture. It takes about a week or ten days to grow on egg media, and produces coiled colonies which are butter yellow in color. If special methods are used, however, it is very simple to dissociate this organism into a smooth (Fig. 7) and a rough form (Fig. 8). The accompanying figures will demonstrate the difference in morphology.

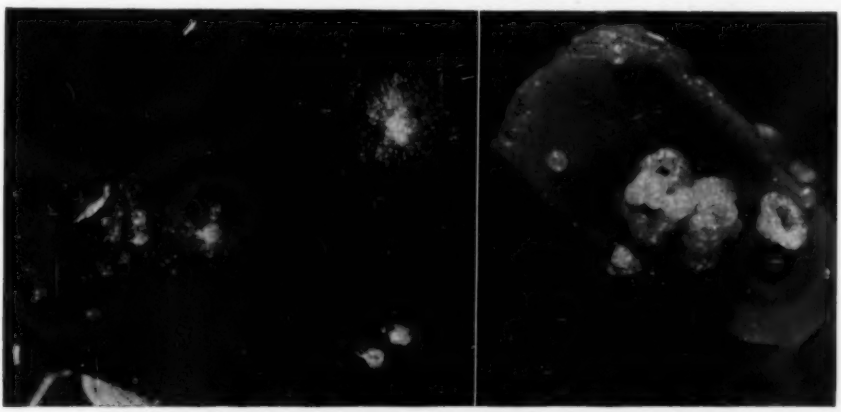

Fig. 7. Fig. 8.

Fig. 7.—Smooth "S" BCG colonies. Note edges sloping into medium (pH 7.2). Age of culture, 20 days. Source, organs of infected animals.

Fig. 8.—Rough "R" BCG colonies on Löwenstein's malachite green egg medium (pH 6.1). This is the twelfth generation from an original blood culture. Age of colony, 5 days. Note the single large granular colonies, the coiled and the craterlike ones composed of similar granules. The demarcation of colony and medium is distinct.

Neither type of colony will produce progressive tuberculosis if inoculated into guinea pigs. We have inoculated thousands of animals, and we have never seen progressive tuberculosis following BCG inoculation. Some of the early work done by Petroff[12] and others,[13] in which they claimed that the dissociate strains were virulent, has not been repeatable since then.

The morphology of the organism is of special interest. It is an acid-fast curved rod much the same as the bovine tubercle bacillus (Fig. 9). Using special methods, including the electron microscope, shadow-casting, and hyper-

tonic solutions, certain characteristics of the organism have been disclosed which are of particular interest. I found (with Dr. C. I. Reed and B. P. Reed) that the bacillus has a definite capsule (Fig. 10), and granules can be found (Fig. 11) which are, most likely, the origin of new bacilli.

BCG is an avirulent bovine tubercle bacillus which retains the cultural and morphologic characteristics of bovine mycobacterium.

Fig. 9.—*Bacillus Calmette-Guérin* showing smooth surface and polar bodies. Electronmicroscopic photo following shadow casting with chromium. (×45,500.)

Fig. 10.—*Bacillus Calmette-Guérin* after shrinking in hypertonic solution and shadow casting. Note definite capsule and shadow cast by irregular surface. (×45,500.)

VACCINATION

Vaccination in Humans.—After numerous studies in animals, and after showing the avirulence of the organism, Calmette and Guérin were still reluctant to use it in humans. It was Weil-Hallé[14] who was allowed by Professor Calmette to use the vaccine first in humans; this was early in 1921, after there had been 230 consecutive transfers from the original strain over a period of thirteen years.

Methods of Vaccination.—The question arose at once as to the best method of vaccinating humans. Since Besredka's influence was strong at this time, it was decided to use the oral route. It was soon learned, however, that the

rate of conversion of the tuberculin reaction following this method of vaccination was very low; if 10 mg. of BCG were given orally on the third, fifth, and seventh day of life, a positive von Pirquet's test occurred in only 15 per cent of the infants after three months. More recently in Brazil, Arlindo de Assis has been using massive doses of vaccine by mouth.[16] He has given as much as 90 mg. in the first 10 days of life, and has reported 83 per cent positive reactors after the fourth month (though he used 10 mg. of O. T. as a test dose).

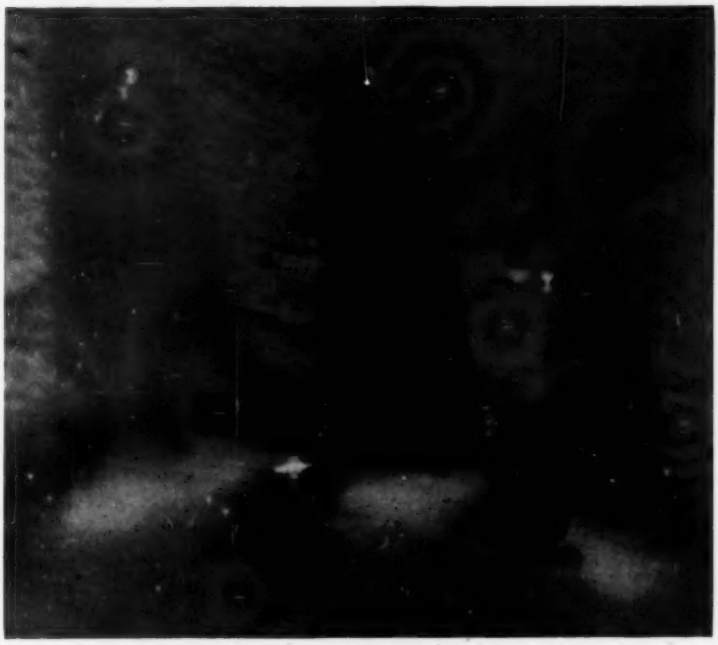

Fig. 11.—*Bacillus Calmette-Guérin.* Same treatment as in Fig. 10. Note definite granules. (×45,000.)

Weill-Hallé,[17] using the subcutaneous method, obtained 100 per cent conversion after nine weeks by the administration of from .02 to .04 mg. of vaccine. Unfortunately, there were many complications, including cold abscesses which persisted for long periods of time. Wallgren[18] later suggested and used the intradermal route, and this method produced a high degree of conversion; superficial ulcers occurred in a high percentage of the cases, however, and if the vaccine was not administered properly, small abscesses occasionally resulted. One must be extremely careful with this method in order to avoid complications. Wallgren, using 0.1 mg., noted 100 per cent positive reactors after seventeen weeks.

In an effort to avoid complications, I described the scarification method of multiple punctures in 1937.[19] The principle of this method was the introduction of minute doses of vaccine at multiple sites into the superficial layers

of the skin transcutaneously, rather than a single large dose intradermally, which so often leads to necrosis and slough. In the original procedure a drop of vaccine was placed on the skin, and thirty punctures were made with a sewing-type needle through the vaccine into the skin over an area 3 × 1½ cm. square.

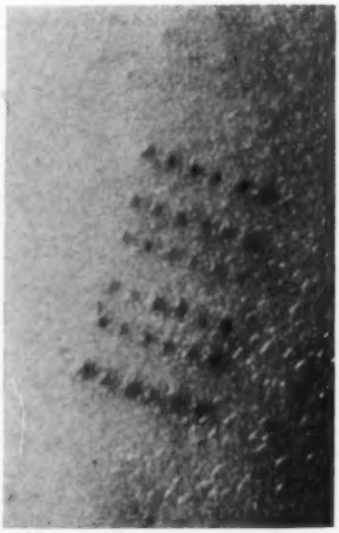

Fig. 12.—Papules ten days following vaccination in a young adult. Note discreteness.

Recently we have developed a stainless steel disk 1 inch in diameter in which there are thirty-six prongs and which can be controlled by a small magnet.[20] The entire vaccination is accomplished with one pressure. A week or so after this method is used, small 2 to 3 mm. papules develop (Fig. 12), remain stationary for from two to three weeks, then regress and heal without gross evidence of scarring. In infants the lesions are minute, about 1 mm. in diameter, and sometimes difficult to see; in fact, the mother rarely knows on which arm the child was vaccinated. The draining lymph nodes may become slightly enlarged, and may be palpated if a special effort is made. They never enlarge to become grossly visible, and never break down. The original method is modified in France[21] by making numerous scratches through a drop of vaccine, and in New York by the spring-actuated multiple puncture apparatus of Birkhaug.[22]

Technique of Using Multiple Puncture Disk.—Cleanse the skin over the deltoid region of the left arm with acetone and allow it to dry thoroughly. Place a drop of vaccine on the arm with a capillary tube or from an ampule (Fig. 13). Grasp the disk with the alcohol-cleansed metal plate of the magnet, allowing the wide margin of the disk to extend beyond the magnet and away from the operator. It should be held at a 30 degree angle. Tap the drop of

vaccine with the wide margin of the disk, and pull it along so that an area 2.5 cm. in diameter is covered with vaccine. Dip the points of the disk into the vaccine, rotating the disk slightly so that the points become moistened.

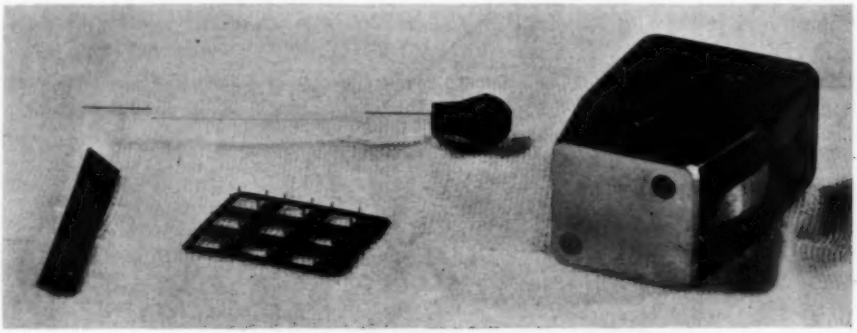

Fig. 13.—The "set up" for vaccinating. Note saw, capillary tube with vaccine, disk, and magnet.

Fig. 14.—Method of using multiple puncture disk. Note position—holder in palm just beneath the index finger, and the other hand grasping the arm underneath, and tensing skin. The disk is held in place by magnetic plate.

Place the disk in the center of of the vaccine and move the metal plate of the magnet so that it is now centered on the disk. This will avoid bending the metal. With the butt of the magnet in the palm, just beneath the index finger, and with the other hand grasping the arm underneath and tensing the skin appreciably (Fig. 14), apply pressure so that the points of the disk are well buried in the skin. In adults considerable pressure is used, whereas in newly born and older infants only enough pressure is applied so that the penetration of the points is readily felt through the palm of the operator's hand.

With the pressure still exerted as above, rock the magnet and disk forward and backward and from side to side several times. Be sure to maintain the original pressure. At this point release the grasp on arm and slide the

magnet away, off the disk, and toward the operator, maintaining the pressure, though slightly less than originally. Following a successful procedure the disk remains on the arm, lying flat, with the points still buried in the skin. If the points are on top of the skin, then the procedure must be repeated. With the thumb and index finger, grasp the disk at the edge opposite the wide border and gently lift it away from the skin. There should be a feeling of the points disengaging themselves from the skin. Tap the vaccine again with the wide margin of the disk so that each perforation of the skin is covered with vaccine.

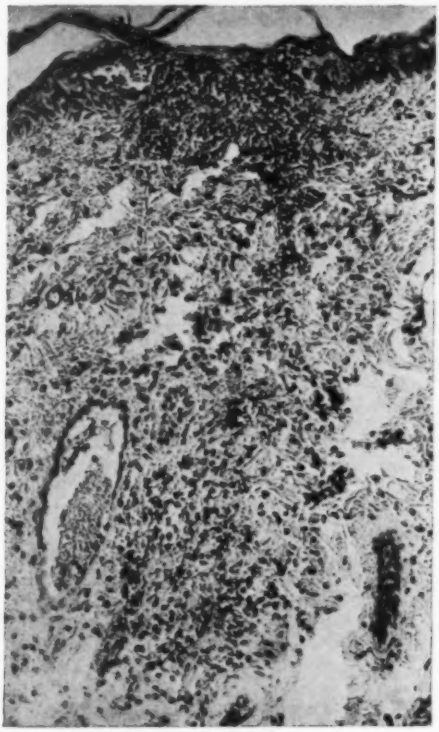

Fig. 154.—Site of injection following multiple puncture technique. Note minute lesion just beneath epithelium and absence of dilated polymorphonuclear-filled lymphatics. (Guinea pig skin, five hours after injection.)

Do not use much pressure, since it will press the vaccine out of the perforations. Allow the vaccine to dry on the arm without dressing. Do not wash the arm for twenty-four hours. No other precautions are necessary. The disks are inexpensive and may easily be sterilized by boiling.

The microscopic lesions produced by the multiple puncture method are of interest in that the vaccine enters into the most superficial layers of the skin, usually just beneath the epidermis. Since only small doses are delivered at any one point, there is never any abscess formation. Because the vascular

supply at this level in the skin is relatively great and the cells of the reticulo-endothelial system are most numerous, many tubercle and giant cells form (Figs. 15, *A* and *B*).

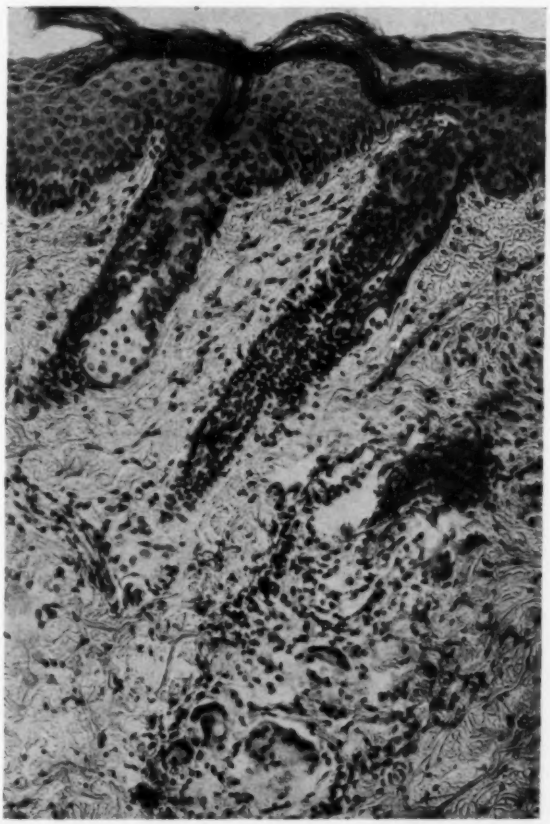

Fig. 15*B*.—Numerous giant cells and histiocytic proliferation, ten days after injection.

In contrast, it is almost impossible to inject material by intradermal injection as superficially as by the transcutaneous method, and the vaccine is introduced by that method into the portion of the skin which is poor in blood supply and reticulo-endothelial cells. Because of the relatively large dose at one point a small area of necrosis forms which is surrounded by a cuff of pus cells which partially occludes the lymphatics and further favors central necrosis (Figs. 16, *A* and *B*). Since this necrotic material must either be extruded or absorbed, ulcers form unless absorption takes place.

The Rapidity of Development of Tuberculin Reactions.—It is possible to produce a positive tuberculin test in guinea pigs in from one to two weeks following a single puncture through a drop of vaccine.[23] In newborn infants,

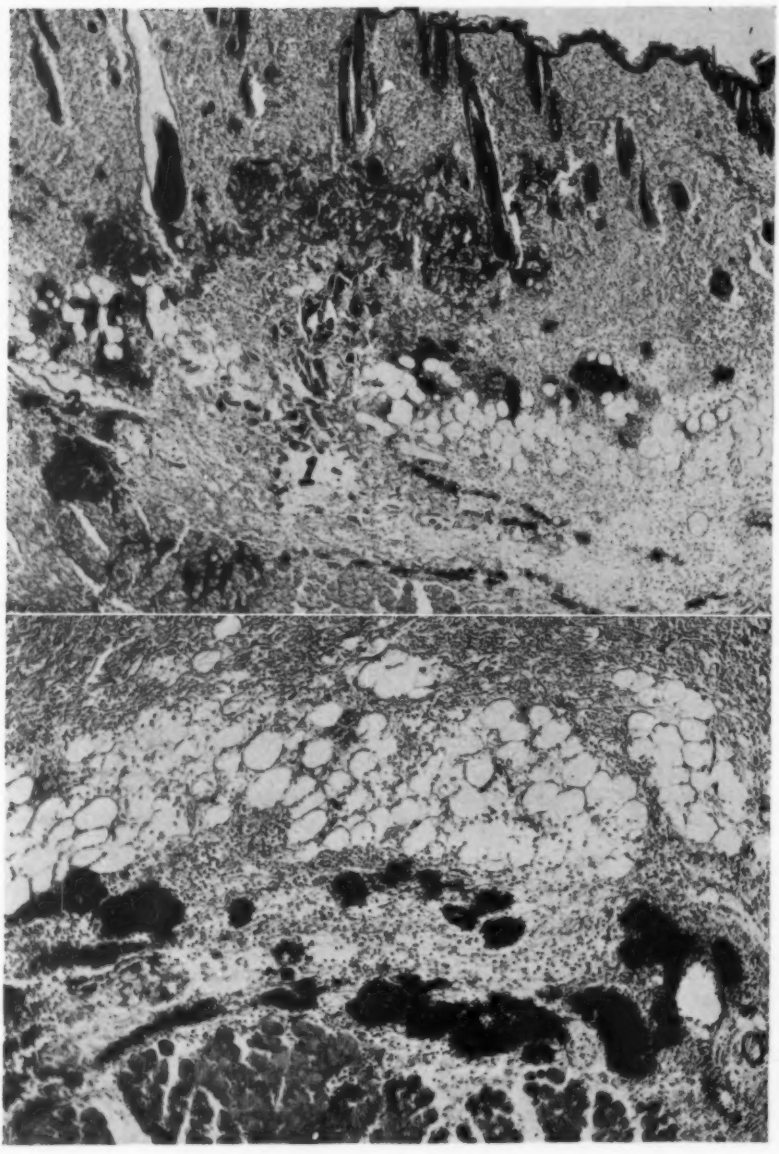

Fig. 16.—*A*, Site of injection following careful superficial intradermal inoculation (guinea pig). Note that center of lesion is deep in the reticulum layer and necrotic (*1*); and a broad zone of polymorphonuclear infiltration surrounds site (*2*). (Four hours after injection hematoxylin and eosin ×80.)

B, Edge of lesion showing in (*A*). Note that the polymorphonuclear cells are in dilated lymphatics. (Hematoxylin and eosin ×180.)

children, and adults we have tried from thirty to ninety punctures, and varying concentrations of vaccine, but at the present time we employ the multiple puncture disk and vaccine which contains 15 mg./ml. moist weight of organisms. Positive tuberculin reactions appear as early as eleven to thirteen days following vaccination in infants, and they are almost universally positive at one month. We may get as high as 90 per cent conversion in older children and adults in two weeks' time. The complications following this method are practically nil.

Immunity Following Vaccination.—I will not go into the literature deeply in discussing the immunity conferred by BCG vaccination. All of you are familiar with the excellent work of the Scandinavians,[24] the French,[25] the Americans,[26] and a host of others all over the world. Up to the present time there have been almost 40 million vaccinations performed, 30 million in Japan alone.[27] The number done in Russia is not known, but it would probably greatly enlarge these figures. There is unanimity in practically every report that a definite reduction in the morbidity and mortality of tuberculosis follows BCG vaccination. Many of the reports have been criticized because of the lack of controls.

We have tried to set up experiments in Chicago which would meet all the criticisms concerning controls which have been made in the past.[28] In this study our control group subjects have been selected in as unbiased a manner as we think possible. These infants were exclusively from tuberculous families. They were referred to us by the Chicago municipal tuberculosis clinics and by private physicians and clinics. The diagnostic data and the results of the sputum examination of the tuberculous contact were submitted, and all x-rays were reviewed by our clinic before the diagnosis was accepted. With the birth of the child, immediate separation was arranged if the mother was tuberculous; if other members of the family were tuberculous, the child was allowed to stay in the hospital as long as the mother was there. In every case the child was then placed in one of our own foster homes. Visits to the foster home were made by our pediatrician every week. The vaccination or placebo was done in the foster home.

The duration of isolation ranged from six weeks to four and one-half months, depending upon the type of case. Where the mother had far advanced disease and a positive sputum, for example, the child was not vaccinated until three months after birth, providing there was a negative x-ray and a negative tuberculin test. When it was the father who was tuberculous, the child was vaccinated three to seven days after birth.

Infants were usually returned to their homes six weeks after vaccination, provided the Mantoux test had become positive in vaccinated individuals, or if it was negative in children who were controls and there was no open source case. Eighty per cent were returned in this manner.

The division of cases was done by a master chart. The doctor who did the vaccinating never made the choice as to whether the child was to be a control or vaccinated. The cases were strictly alternated in categories determined by

the types of source cases. Children who were to return to a tuberculous environment were vaccinated with twice the dose used for the noncontact infants (i.e., two series of thirty punctures with the straight needle, or, more recently, a series of two disk punctures).

Progress of the infants was followed by means of clinic visits at approximately six-month intervals; they were then tuberculin tested, x-rayed, and the amount of contact which they had had during the preceding period was ascertained. Between the clinic visits the infants were seen at intervals by a nurse in the home.

It may be seen in the table that there were 139 infants in the vaccinated group and 128 in the control group. There were practically the same number of vaccinated and control group infants in each category (Table I), according to the type of tuberculosis in the source case. The amount of actual contact was similar, though the vaccinated group had the more contact (186 person years contact with the mother in the vaccinated group as against 160 in the controls) (Table II).

TABLE I. SOURCE OF CONTACT AND TYPE OF TUBERCULOSIS AT BIRTH OF CHILD

CONTACT SOURCE	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		POSITIVE SPUTUM	
	VACCINATED	CONTROL	VACCINATED	CONTROL	VACCINATED	CONTROL	VACCINATED	CONTROL
Mother (Alone or with others)	11	11	43	41	33	36	27	24
Father (Alone or with others)	10	9	18	17	17	14	14	14

Following vaccination there was 100 per cent tuberculin conversion, and this remained constant for almost five and one-half years (Table III). In the control group the number of individuals at each age was practically the same as for the vaccinated. For example, at birth there were 131 and 128, respectively; at 19 to 24 months, there were 102 and 100; and at 61 to 66 months, there were 40 and 40.

The degree of exposure is evident when it is noted that at 61 to 66 months, 57.6 per cent of the nonvaccinated control group infants reacted to tuberculin (Vollmer patch test) (Table IV). The amount of contact must have been great since in our so-called noncontact group only 32.9 per cent of the infants had a positive reaction at that age, and this noncontact group of infants lived in the most heavily infected district of Chicago.[28]

TABLE II. AMOUNT OF CONTACT WITH PULMONARY TUBERCULOSIS

	VACCINATED	CONTROLS
Continual, with mother	186.5 person-years	160.1 person-years
Average	2.8 years	2.6 years
Continual, with father	72.2 person-years	73.1 person-years
Average	2.8 years	3.3 years
Continual, with others	11.9 person-years	25.1 person-years
Average	1.3 years	2.5 years
Intermittent, with any	37.3 person-years	56.2 person-years
Average	2.2 years	2.4 years

TABLE III. TUBERCULIN REACTIONS FOLLOWING A SINGLE VACCINATION IN THE CONTACT GROUP OF INFANTS

AGE (MO.)	NO. REGISTERED	NO. TESTED	NO. POSITIVE	% POSITIVE
0-3	131	124	124	100
4-7	123	116	116	100
8-12	118	107	107	100
13-18	111	95	95	100
19-24	102	87	87	100
25-30	91	77	77	100
31-36	78	69	68	98.6
37-42	72	59	58	98.3
43-48	63	52	51	98.1
49-54	54	43	42	97.7
55-60	48	36	35	97.2
61-66	40	27	26	96.3

TABLE IV. TUBERCULIN REACTIONS IN THE CONTACT CONTROL GROUP OF INFANTS

AGE (MO.)	NO. REGISTERED	NO. TESTED	NO. POSITIVE	% POSITIVE
0-3	128	128	0	0
4-7	124	120	9	7.5
8-12	115	110	20	18.2
13-18	109	100	41	41
19-24	100	91	45	49.5
25-30	93	83	46	55.4
31-36	86	75	42	56
37-42	79	70	41	58.6
43-48	73	64	36	56.3
49-54	66	53	31	58.5
55-60	52	43	24	55.8
61-66	40	33	19	57.6

There were twice the number of cases of tuberculosis in children in the control group as among the vaccinated (six cases against three) (Table V). What is more significant is the fact that only one child from the vaccinated group needed hospitalization, while four from the control group required it! Indeed, in the vaccinated group, two of the children were diagnosed as tuberculous only because of calcified lesions in the lung; the third showed a small area of infiltration in the left hilus which calcified in a short period of time.

TABLE V. INCIDENCE OF TUBERCULOSIS IN THE CONTACT GROUP OF CHILDREN

	VACCINATED	CONTROLS
Total number of children	131	128
Person-years observed	459	459
Cases of tuberculosis		
Total number	3	6
Rate*	6.5	13
Children hospitalized		
Total number	1	4
Rate*	2.2	8.7
Deaths from tuberculosis		
Total number	0	3
Rate*	0	6.5
Deaths from other causes		
Total number	2	2
Rate*	4.3	4.3

*Rate per thousand person-years observation.

On the other hand, three of the six children in the control group died. All were autopsied and were found to have a typical primary lesion in the lung with spread to the hilus lymph nodes; in one case there was a miliary tuberculosis and tuberculous meningitis. These features are most striking, since it appears that BCG vaccination may prevent virulent tubercle bacilli from establishing themselves in the host, or if the infecting dose is large and they do get a foothold, their spread from the site of entrance is inhibited. It is much the same as I have described in experimental animals.

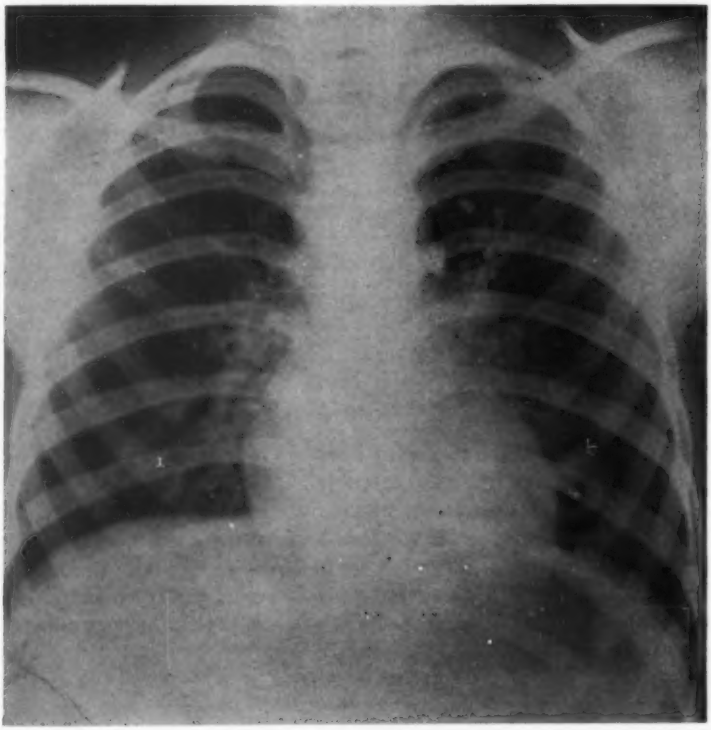

Fig. 17.—D. F., a white female child vaccinated at 5 weeks of age. X-ray taken at 5 years of age. Mother and father both tuberculous. Continuous contact after two months in foster home. Note typical calcified primary in left upper lobe.

In a recent discussion (1948) with Dr. Sigrid Holm of Copenhagen, she informed me that for the past eight years in their series there has not been a case of tuberculous meningitis in infants who have had successful vaccinations. In one of Dr. Wallgren's reports[24a] he mentions that since the inauguration of BCG vaccination in Gothenburg, over a period of three years (1942 to 1945) there was not a death from tuberculosis in infants under one year of age. This is strong evidence that BCG not only prevents primary infection to a large

Fig. 18.—F. R., Negro male child, aged 2 years (vaccinated at 12 days of age). Note infiltration in right lower lobe. Source case, two older children. Continuous contact after six weeks in foster home. His sibling, a control group child, died from tuberculous meningitis.

Fig. 19.—Same case as Fig. 18; aged 2 years, 7 months. Note early calculation in right lower lobe.

extent, but when primary infection does occur, there is less possibility that it will spread hematogenously to other parts of the body. This latter chance is the dreaded and serious aspect of primary tuberculosis.

I have recently completed a study of progressive primary tuberculosis in young adults and have shown that there is miliary spread in practically every instance, as shown by post-mortem examination and histologic study.[29] This is also considered to be the course in infants and children.

The question always arises as to whether the type of pulmonary lesions in infants and children who react to tuberculin and are reinfected is different as compared to those who do not originally react to tuberculin. From the x-ray films (Figs. 17, 18 and 19) it is difficult to note any striking difference in the end results. The important feature is that there is more likelihood of healing and calcification in the vaccinated group than there is in the control group. Thus it is evident that BCG vaccination does largely prevent primary infection and the sequelae to primary infection.

BCG should not be considered a panacea for prevention of tuberculosis. Massive reinfection will break down immunity to most vaccinations. The most important factor in the prevention of disease is removing the source of infection. This is especially true of tuberculosis. BCG should be administered in tuberculous households only if there is separation before and after vaccination. An infant under a year of age is so easily infected that without isolation BCG is not recommended. It is hard to understand why we should expect more of BCG, let us say, than of typhoid or smallpox vaccination, where in the former stringent efforts are made to minimize the source of contamination, and in both strictest isolation is practiced.

SUMMARY

From experimental work in animals in my laboratory, as well as from clinical studies by my associates* and myself over a period of fifteen years, I can say unequivocally that BCG is harmless and has definite value in preventing primary infection. It also minimizes the hematogenous sequelae which may follow primary infection, including tuberculous meningitis, miliary tuberculosis, etc.

BCG vaccination is an important adjunct to the accepted methods of tuberculosis prevention, such as early diagnosis and isolation of the source case. BCG vaccination should not be expected to do more than other forms of vaccination in which all attempts are made to eliminate the source of contagion.

A strictly controlled study is presented of infants born of tuberculous parents. Isolation was practiced after birth in the control group infants and vaccinated infants alike. There were 131 vaccinated infants who were followed for 459 person-years, and 128 control group infants followed for 459 person-years.

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In the vaccinated group there were three patients with roentgenographic evidence of tuberculosis; one was hospitalized and recovered. All showed calcification by roentgenogram.

In the control group there were six children, four of whom were hospitalized, and three of whom died of generalized tuberculosis.

BCG vaccination not only decreased the incidence of primary tuberculosis but also staved off the progression and generalization of the process when infection did occur. The multiple puncture method of vaccination is recommended, since it is simple to apply, is devoid of complications, and has produced universal and lasting (at least five and one-half years) conversion of the tuberculin reaction when applied to newborn infants.

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DEATH OF CESAREAN INFANTS: A THEORY AS TO ITS CAUSE AND A METHOD OF PREVENTION

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THE deaths of two infants delivered by cesarean section in the summer of 1946 stimulated our interest in the problem of the cesarean infant. In our experience these infants have had a more stormy time than have those delivered normally.

Bloxsom[1] has stated that in his experience infants delivered by cesarean section present peculiar difficulties of respiratory onset. His thesis, based upon a series of 100 infants delivered by cesarean section, is that a test of labor decreases the incidence of post-section asphyxia by 25 per cent and that failure to condition the infant by uterine contractions or passage through the birth canal is responsible for many cases of asphyxia.

We have had similar experiences with cesarean babies but we have been more impressed by the group in whom the adverse symptoms do not appear immediately but are seen from two to four hours later.

These infants leave the operating room in apparently good condition. Later they develop cyanosis, respiratory distress with dyspnea, air hunger, and costal retraction with rapid weak pulse. They fade rapidly and die in terminal convulsions in about eighteen to twenty hours. At the first sign of distress oxygen was started, the infants were placed in incubators, Coramine, caffeine, and Adrenalin were given, according to the judgment of the physician. These measures were seldom of benefit.

Our observations correspond to those of Potter,[2] whose description follows: "There is one syndrome, not commonly recognized, which makes its appearance a few hours after birth. It is most common following cesarean section although it occasionally accompanies other methods of delivery. The infants usually breathe spontaneously and appear normal for a few hours. Subsequent respiratory distress gradually makes its appearance. Costal retraction, irregular or shallow breathing, variable cyanosis, muscular twitching, and even convulsions may occur. The infants survive at times, but when death follows, the only pathologic lesion that we have observed in the majority of these infants is an increase in the cerebrospinal fluid within the subarachnoid space around the brain. Clifford believes this fluid is the result of anoxia and has described it as occurring in infants who were delivered by cesarean section because of maternal hemorrhage from placenta previa. We have not observed it in the great majority of infants who have had definite evidence of intrauterine anoxia and believe, in our series at least, it is definitely related to delivery by cesarean section, rather than to the condition for which the operation was performed. The actual method by which it is produced and any method of prevention are both unknown. Death appears to result from increased intracranial pressure."

Potter and Rosenbaum[3] have ascribed the same clinical picture of extreme respiratory distress developing a few hours after cesarean delivery, to a specific intracranial lesion. This condition, not limited to infants of any particular fetal age, consists of an abnormal increase in cerebrospinal fluid which the authors have termed "meningeal edema." Since Potter has not observed the same meningeal state in definitely anoxic deaths, she believes that it is attributable to the type of delivery rather than to any anesthetic or anoxic hazard. Lund has seen the same course of events as has Smith of Boston Lying-In Hospital.

Russ and Strong[4] describe a clinical picture of asphyxia responsible for death in almost 9 per cent of infants born by cesarean section. The typical infant was one who was not in apparent respiratory difficulty upon delivery but developed repeated attacks of cyanosis and increasing respiratory distress after from two to three hours of apparently satisfactory breathing. The authors are not sure of the relationship of all this to the operative birth and apparently do not consider it due to the anesthesia. The resulting deaths were believed to be due to aspiration pneumonia. They advise routine intratracheal catheterization of the newborn infant immediately following delivery, stating that from 3 to 7 c.c. of the mucoid material is aspirated from cesarean babies as compared with 1 or 2 c.c. obtained from the average newborn infant delivered through the normal birth channel. By this technique their infant mortality was reduced from 8.7 per cent to 1.8 per cent in their series of 137 cesarean babies.

Gellis, White, and Pfeffer[5] have introduced the procedure of gastric suction to prevent the syndrome of delayed respiratory difficulty. They feel that it might be due to the ingestion of large amounts of amniotic fluid, followed by regurgitation and aspiration.

Twenty-five babies of diabetic mothers delivered by section were studied to determine the effect of gastric suction on the frequency of these signs. After initial gastric suction this procedure was done every three hours for twelve hours. From 10 to 20 c.c. of fluid were obtained at the first aspiration on the average, and at times as much as 30 c.c. As a control group, twenty-five babies of diabetic mothers delivered by section were not treated by gastric suction.

Of the twenty-five infants treated by gastric suction, only four showed respiratory symptoms. These symptoms were mild and were present at the time of birth. In the control group six had respiratory difficulties at birth and nine developed symptoms later on. The severity of the respiratory embarrassment was much greater in the control group.

Because of the more favorable course of their infants treated by gastric suction, Gellis, White, and Pfeffer suggest that this procedure be done additionally on all infants delivered by section.

Potter and Adair[6] report a mortality rate of 8.7 per cent in a series of 1,462 sections.

From these figures from the various reports quoted it is seen that our experiences with infants delivered by cesarean section are not unique. It is likewise evident that there is a well-defined clinical syndrome in many of those babies who do not survive.

Usually at the time of cesarean section as soon as the uterus is opened the operator delivers the infant as rapidly as is consistent with the infant's safety. The cord is clamped and cut immediately and the infant is handed to the waiting assistant. Quoting directly from DeLee and Greenhill[7]: "Amniotic fluid gushes out while the operator searches for one foot by means of which he performs breech extraction with the Mauriceau maneuver on the after-coming head. Now 10 units of pituitary extract are given intramuscularly. The assistant presses the sides of the abdomen against the retracting uterus to keep amniotic fluid and blood out of the peritoneal cavity. Clamping the cord in two places and cutting between requires only an instant, and the operator hands the child to an assistant who stands at his elbow bearing a large tray covered with a sterile blanket." This is in marked contrast to the procedure during normal or vaginal delivery. At this time the cord is not clamped and severed until pulsations have ceased. While the uterus is contracting down and the cord is pulsating, a considerable amount of blood is being propelled into the newly born infant's circulation.

It occurred to us that part of the cesarean infant's difficulty might be explained by the deprivation of a considerable amount of the blood due to the rapidity of tying off of the cord, which the baby delivered in the normal manner receives. The symptomatology resembles that of hematogenic shock which will be discussed hereafter.

Ballentine,[8] from his studies of delayed clamping of the umbilical cord in newborn infants, found an average increase of 96 c.c. of blood by delaying clamping until cord pulsations had ceased.

De Marsh, Windle, and Alt[9] found that immediate clamping of the cord of the newborn infant deprives the infant of 107 c.c. of blood (on the average). They found that the average blood volume of those infants allowed to receive this placental and umbilical vessel blood (delayed clamping) was 361 c.c. or 11.8 per cent of the body weight; it was only 301 c.c. or 9.6 per cent of the body weight when immediate clamping of the cord was practiced. The average quantity of blood flowing freely out of the placental end of the severed cord was 107 c.c.

These investigators estimate that more than 26 per cent, but less than 34 per cent of the average total fetal blood is in the placenta and umbilical vessels at the end of fetal life. Under normal conditions of birth most of this blood passes to the newborn infant during the third stage of labor while the uterus is contracting on the placenta.

These figures show that the quantity of blood that the infant receives from the placenta (from 96 to 107 c.c.) looms tremendously large in relation to its total blood volume.

The thought occurred to us that the immediate clamping and cutting of the cord might be the essential point of difference between the cesarean- and the normally delivered infant. This procedure (the immediate clamping and cutting of the cord) unquestionably deprives the infant of considerable blood and can

well be the cause of the previously described delayed reaction. For this reason it was decided to change the technique of our cesarean sections to enable the infant to receive more placental blood.

The assistant designated to care for the infant is scrubbed and stands to the left of the operator. After the infant is delivered from the uterus this assistant holds the infant by the legs with the head down. The pharynx is aspirated by means of a rubber bulb syringe. The cord is neither clamped nor severed. The placenta is separated from the uterus and wrapped in a large turkish towel. Several clamps are used in order to secure the placenta as it slips out easily. The infant and the wrapped placenta connected by the intact umbilical cord are carried to an awaiting table or cart. The placenta is suspended from a standard by means of a clamp attached to the towel. The infant lies on the table wrapped in sterile cloths and warm blankets. The stimulants of choice are in readiness, as is an infant resuscitator. The cord is not cut until its blood vessels have collapsed. It is then clamped, cut, and tied in the usual manner. The placenta is usually drained and the cord collapsed in from six to ten minutes.

By this technique we feel that the infant receives much more blood than he would were the cord cut early. In several instances the placenta was weighed before and after suspension. The average difference was 45 grams. This amount is undoubtedly conservative as the infant receives blood constantly at the operating table while he is suspended with the head down and while he and the placenta are being transported to the awaiting infant's table. On one occasion the umbilical cord was accidentally severed on opening the uterine cavity. The cord was clamped immediately. Ninety-five cubic centimeters of blood were recovered.

We assume that the amount of blood saved for the infant by this technique to be about 90 c.c. This represents a transfusion of a considerable amount, considering the blood volume of the newborn infant to be approximately 10 per cent of the body weight.

DISCUSSION

From our observations we feel that the immediate clamping and cutting of the umbilical cord deprives the newborn cesarean infant of a considerable amount of blood. The clinical course of these infants is similar to that of older patients in shock from blood loss. If the blood deprivation is beyond a critical point, symptoms of secondary or delayed shock may appear two to four hours later consisting of grunting shallow respirations, air hunger, cyanosis, costal retraction, and terminal convulsions. These are similar to those observed in the older child or adult in shock from blood loss.

We are of the opinion that the crucial point of difference between the normally delivered infant and the cesarean-delivered infant is in the handling of the umbilical cord and placenta of the cesarean infant. The immediate clamping and cutting of the umbilical cord deprives the infant of blood which he would ordinarily receive under conditions of normal delivery.

The differences between the normally delivered and the cesarean-delivered infant may be summarized by the following table:

TABLE I

	NORMAL DELIVERY	CESAREAN DELIVERY
Uterus (During active labor) Alternate contraction and relaxation	Conditions the infant for extrauterine respiration[1]	Lacking
Uterus: Final contraction phase	Extra blood from placenta to infant	Lacking
Passage of infant through vagina and pressure on infant at end of second stage of labor	Squeezing effect may result in discharge of fluid from respiratory tract	Lacking
Position of infant after delivery	Dependent: Gravity may favor blood flow toward infant	Elevated: Gravity may favor blood flow from the infant to the placenta

Since instituting this technique our results with our cesarean babies have been much better than formerly. For this reason we have not felt justified in running a control series. The secondary shock phase has not been observed since the change to this technique. Consequently we have not found it necessary to use plasma or blood intravenously in the treatment of this condition.

In eighty-seven sections done since instituting this technique of placental suspension and drainage, there have been no instances of the previously described syndrome. One infant delivered by cesarean section from a mother with far-advanced tuberculosis died several hours later without any of the symptoms of shock. This child's condition had not been good at any time. Death was thought to be due to prematurity and to the influence of the mother's toxic condition. There was one other death on the fourth day from atelectasis.

The infants delivered since using this technique have impressed us as being more active sooner than the average section infant. They are ruddy in color. There have been few neonatal upsets.

This series includes one premature infant delivered by section because of placenta previa. This child survived. One other premature infant was delivered by section because of uteroplacental apoplexy. This child also survived.

We feel that this procedure is especially valuable for premature infants. Just as delayed ligation of the umbilical cord is important to the premature infant in normal delivery, we feel that the procedure of placental suspension and drainage is likewise important to him in cesarean section. Since the placenta is larger in relation to body size in the premature than in the mature baby, the quantity of the placental blood is greater in relation to the premature infant's blood volume. The premature infants in this series have done well. We expect to make a more complete report on the premature group of infants later.

We have been impressed by the resemblance between this syndrome of the cesarean infant and that of hematogenic shock in the older patient. Common points of similarity include accelerated weak pulse, subnormal temperature, the presence of dyspnea, cyanosis, and vomiting. It has not been possible to determine blood pressures, blood volumes, and circulation times on these infants.

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CONCLUSIONS

1. A theory of hematogenic shock as a contributing factor in the mortality of babies delivered by cesarean section is postulated.

2. The immediate clamping and cutting of the umbilical cord is thought to be the etiological factor by depriving the infant of a variable amount of placental blood.

3. The technique of placental suspension and drainage for the prevention of hematogenic shock in the cesarean-delivered infant is described.

4. In a series of eighty-seven sections since instituting this technique no instances of "delayed shock" have been encountered.

All of these sections were done at St. Elizabeth Hospital and Levering Hospital, Hannibal, Mo.

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GALACTOSE DIABETES (GALACTOSEMIA)

A Clinicopathologic Study of Two Siblings

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THE inability to metabolize galactose normally is a rare and fascinating metabolic anomaly. While this abnormal metabolism of galactose has serious effects on growth and development, the process may be reversed, if diagnosed early, by removal of galactose from the diet. The essential features of this syndrome include severe malnutrition, hepatomegaly, and galactosuria. Mental retardation and lamellar cataracts have been less constant findings, perhaps related to the severity and duration of the process.

The purpose of this report is to present the clinical records of two siblings with galactosemia, and to present a new concept of the clinical and pathologic sequences of this disease.

REVIEW OF THE LITERATURE

This syndrome was first described by Von Reuss in 1908.[1] The infant weighed less at 8 months of age than at birth; he had hepatomegaly, splenomegaly, and galactosuria which disappeared when milk was omitted from the diet. Autopsy revealed hepatic cirrhosis. Von Reuss emphasized that an alcoholic etiology could not be ruled out, since the infant he described had been given cognac daily since birth.

The next report in 1917 was that of Göppert,[2] who described the syndrome in four siblings. Two of the infants died within the first two months of life. The third was alive at 6 years of age but was frail and had an enlarged liver. Urinary excretion of galactose was demonstrated in the fourth child. At the age of 3 years there was hepatomegaly, and growth was retarded.

Fanconi[3] in 1933 reported on a case of galactose diabetes in a 9-year-old boy. This patient demonstrated a less severe form of galactose intolerance though his blood galactose reached 466 mg. per cent. He was also afflicted with diffuse neurofibromatosis.

In 1934 Unshelm[4] recorded another instance of galactosuria occurring in a female infant. The pronounced hepatomegaly disappeared when milk was removed from the diet.

Mason and Turner[5] reported the first case in the American literature in 1935. Their patient was a 6-year-old Negro boy who showed malnutrition, hepatosplenomegaly, and cataracts. There was osteoporosis, and laboratory examination showed galactosuria, albuminuria, and a positive direct van den Bergh reaction. Elimination of milk from the diet produced striking improvement. Studies of the patient's metabolism of carbohydrates showed galactosemia and a subnormal level of glucose in the blood. Injection of epinephrine

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caused a rise in the glucose of the blood but did not affect the level of galactose. Injection of insulin produced an elevation of galactose, while the level of glucose fell in a normal manner.

In 1943 Norman and Fashena[6] described an 11-year-old child with similar clinical findings. This patient showed abnormal retention of Bromsulphalein. After elimination of galactose from the diet there was clinical improvement, and the Bromsulphalein excretion was normal.

Mellinkoff and his co-workers[7] in 1945 described this syndrome in a 2-month-old infant. There was a positive cephalin flocculation test. After removal of milk from the diet this test gave normal findings. In the same year Bruck and Rapoport[8] described the youngest patient reported to date. The infant was 7 weeks of age and had bilateral cataracts. These lenticular opacities disappeared completely after dietary change. These authors suggested that the extensive pathologic changes noted in the disease were the result of toxic effects of galactose on the various tissues.

In 1946 Goldbloom and Brickman[9] recorded two additional cases. Both patients had cataracts and one was mentally retarded.

Evidence of hepatic injury, as shown by an elevated thymol turbidity reaction and lowered prothrombin concentration, was present in the case reported by Goldstein and Ennis[10] in 1948. These tests were not repeated after the child had responded clinically to the elimination of dietary galactose.

Greenman and Rathbun[11] in 1948 did the first intravenous galactose studies on an 18-week-old infant with this disease. They demonstrated increased tolerance to galactose following the acceleration of the metabolism of glucose by insulin and glucose, given together or separately. These authors recommended a high-carbohydrate diet in addition to restriction of galactose in these cases.

CASE REPORTS

CASE 1.—K. L., a white female infant, was born at term on Dec. 5, 1947. Birth occurred after eighteen and one-half hours of labor; there was a low-forceps delivery. The infant's weight at birth was 3,225 grams. Both parents were in normal health. The father, a truck driver, was 23 years of age and the mother was 20 years of age. Both were Rh positive and their serologic tests (Kolmer and Kahn) were negative. The father had had infectious hepatitis two years previous to this date.

The infant appeared to be normal at birth and was discharged from the hospital on the third day after birth. An evaporated milk and Karo formula was given to her. On the sixth day of life the child began to vomit. On the seventh day hematemesis occurred, and the infant became semicomatose. On admission to the hospital on the same day the patient was deeply icteric. There was evidence of dehydration, and the anterior fontanel was depressed. The patient responded only to painful stimuli. The liver was enlarged and the anterior edge was palpable 1.5 cm. below the right costal margin. The extremities were flaccid. Bilateral subdural and lumbar punctures showed no evidence of bleeding.

Laboratory Examination.—The hemoglobin was 110 per cent (16 Gm. per 100 c.c.) and the red blood cells numbered 5,210,000 per cubic millimeter. The white blood count was 8,350 per cubic millimeter with 75 per cent neutrophilic leucocytes (nonsegmented 4 per cent), 23 per cent lymphocytes, and 2 per cent monocytes. A urine specimen was not examined though the urine was noted to have a dark color. The spinal fluid contained 5 cells per cubic millimeter (4 lymphocytes and 1 neutrophilic leucocyte). The Pandy test gave a 1-plus reaction.

A continuous intravenous infusion of 5 per cent glucose in saline was begun. Penicillin (15,000 units) was administered every three hours and vitamin K (1 mg.) was given every twelve hours. The following day the patient's condition was still poor. Because hematemesis continued, a transfusion (65 c.c. of whole blood) was administered. Death occurred at the age of 8 days. The patient's temperature varied from 37° C. on entry to 39° C. terminally.

An autopsy was performed sixteen hours after death. The liver was enlarged and microscopic examination showed severe diffuse infiltration of almost all parenchymal cells with fat. It did not resemble the livers seen in patients with glycogenosis. Although focal necrosis of some hepatic cells had occurred, there was no cirrhosis. The details of the autopsy will form the basis for a separate report.[12]

CASE 2.—A. L., a white male infant, the sibling of K. L. (Case 1), was born at term on Jan. 3, 1949. Birth occurred after a normal labor of five and one-half hours. The infant appeared to be normal at birth. His weight was 4,135 grams. Because of the death with hemorrhage of the sibling, the child was given vitamin K (1 mg.) at intervals of twelve hours for three days. Oxygen was administered as a precautionary measure for twenty-four hours.

Laboratory Examination.—The hemoglobin was 130 per cent (18.5 Gm. per 100 c.c.), the red blood cells numbered 5,390,000 per cubic millimeter, and the white blood cells numbered 18,000 per cubic millimeter with 85 per cent neutrophilic leucocytes (18 per cent nonsegmented), and 15 per cent lymphocytes. No nucleated red blood cells were found.

The child's course while in the hospital was normal. He was given an evaporated milk and Karo formula and was discharged on the third day after birth weighing 3,935 grams. He was examined daily at home. On the fifth day after birth, the skin and scleras were faintly icteric and the patient began vomiting. There was only slight improvement when the diet was changed to a powdered skim milk formula, and vomiting persisted. One clay-colored stool was noted.

He was admitted to the Mills Memorial Hospital on Jan. 11, 1949, at the age of 8 days. His temperature was 37.0° C. There was slight icterus, and the anterior edge of the liver was palpable 2.5 cm. below the right costal margin.

Laboratory Examination.—The hemoglobin was 140 per cent (20 Gm. per 100 c.c.), red blood cells numbered 5,240,000 per cubic millimeter, white blood cells numbered 14,300 per cubic millimeter. There were 63 per cent neutrophilic leucocytes (3 per cent nonsegmented), 26 per cent lymphocytes, 9 per cent mono-

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cytes, and 2 per cent eosinophilic leucocytes. Examination of the urine showed the absence of bile; other tests were not done. The icterus index was 16. The direct van den Bergh was 1.4 mg. per 100 c.c., and the indirect 13.8 mg. per cent.

The following day (January 12) the patient's temperature rose to 38.0° C. The liver was larger and its anterior edge was palpable 5.5 cm. below the right costal margin. On Jan. 12, 1949, at the age of 9 days, the infant was transferred to the Pediatric Ward of the University of California Hospital. On initial examination the patient's temperature was 37.5° C. He was apathic and drowsy, mildly dehydrated, and only in a fair state of nutrition. His skin and scleras had a slightly icteric hue. The lymph nodes were not unusual. The ears, nose, and throat were normal. The heart and lungs were normal to physical examination. The umbilical stump was moist and partially covered by mucoid exudate. The liver was enlarged and its anterior margin was palpable 4 cm. below the right costal margin. It was not tender. The lower border of the spleen was palpable 2 cm. below the left costal margin. The abdomen was soft; it was not tender or distended.

Laboratory Examination.—Laboratory examination on entry showed the following: The hemoglobin was 120 per cent (17 Gm. per 100 c.c.), the red blood cells numbered 6,250,000 per cubic millimeter, white blood cells numbered 14,250 per cubic millimeter. There were 75 per cent neutrophilic leucocytes (7 per cent nonsegmented), 20 per cent lymphocytes, 3 per cent monocytes, 1 per cent basophilic leucocytes, and 1 per cent eosinophilic leucocytes. The red blood cells appeared to be normal. The urine was clear and yellow. The pH was 6.0. There was a faint trace of albumin and an olive reduction with Benedict's solution. There was no acetone, bile, or increase in urobilinogen. Cultures taken from the umbilical stump revealed nonhemolytic *Escherichia coli* and *Staphylococcus aureus* (coagulase positive). Blood cultures showed no growth. Icterus index was 17 units. The direct van den Bergh was 7 mg. per 100 c.c. and the indirect was 69 mg. per 100 c.c. Because of the presence of urinary sugar with the absence of acetone, fermentation tests were done. The urinary sugar was nonfermentable. Barfoed's test was positive, indicating the presence of a monosaccharide. Mucic acid test was positive, indicating the presence of galactose or lactose. Dr. J. F. Oneto of the Division of Pharmacology was kind enough to isolate an osazone by the phenylhydrazine method and demonstrated that it was the galactose osazone which was present. Its melting point was 185° C.

The fasting blood sugar was 218 mg. per cent. When repeated it was 173 mg. per cent of which 144 mg. per cent was nonfermentable reducing substances, presumably chiefly galactose. Galactose tolerance tests were then done (Fig. 1, and Table I). Following the injection of 0.5 Gm. per kilogram of body weight of galactose intravenously there was a rise from 102 mg. per cent to 147 mg. per cent in 15 minutes. This failed to drop appreciably in the next hour, and in 75 minutes it was still 140 mg. per cent. Normally galactose is absent at the end of 75 minutes. At the end of 75 minutes an injection of epinephine was given and produced a rise in blood glucose and total blood sugar and a slight fall in blood galactose (Fig. 1 and Table I). Following each intravenous injection of galactose the infant appeared to be ill, apathetic, and was anorexic. There was fever

reaching 39.6° C. after each injection. Diminishing fever persisted for twenty-four hours. An intravenous glucose tolerance test (0.5 Gm. per kilogram of body weight) was done revealing excellent utilization of glucose with an immediate rise to 235 mg. per cent and a prompt return to 137 mg. per cent in thirty minutes (Table II). No insulin tolerance test was done. A series of hepatic function tests were done (Table III). The thymol turbidity was 5 units. Cephalin flocculation was 1 plus. Total plasma proteins were 5.6 Gm. per cent. Serum albumin was 3.7 Gm. per cent and globulin 1.9 Gm. per cent. The Bromsulphalein test revealed less than 1 per cent retention in 30 minutes.

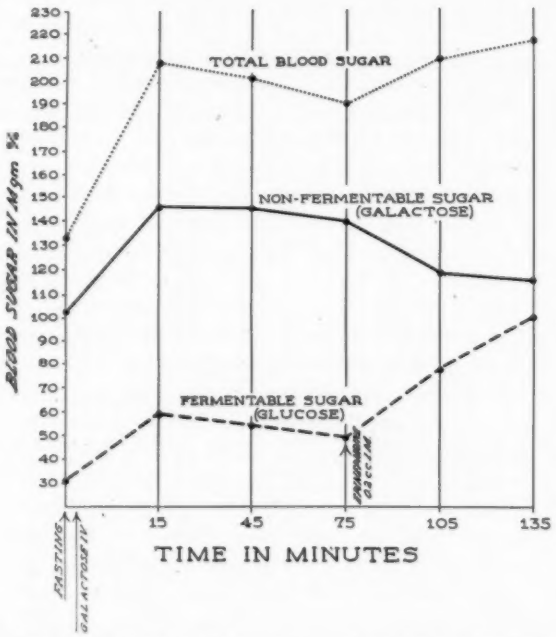

Fig. 1.—Intravenous galactose tolerance test and response of blood sugars to epinephrine. Test performed prior to therapy, with 0.5 Gm. per kilogram body weight of galactose given intravenously (micromethod).

Because of the intolerance to ingested galactose the child's diet was changed from milk to Nutramigen and Dextri-Maltose. Within a few days the urinary sugar and albumin disappeared, and the child started to gain weight.

On Jan. 26, 1949, a biopsy of the liver was obtained with the patient anesthetized with ether. The liver grossly appeared to the surgeon to be normal. Part of the biopsy specimen was analyzed for total lipids and glycogen by Dr. H. W. Elliot of the Division of Pharmacology.* Total lipid extracted with

*Two samples of hepatic tis ue weighing approximately 100 mg. each were immediately weighed and placed in hot potassium hydroxide solution. After hydrolysis, glycogen was determined colorimetrically by the method of van Wagtendonk (J. Biol. Chem. 163: 301, 1946). The duplicate samples each contained 3.3 per cent glycogen.

Only 171 mg. of liver remained for lipid analysis. This was dried at 100° C. overnight, leaving 40 mg. of dry tissue which was powdered and shaken to constant weight with petroleum ether (five extractions). Ten mg. of the original 40 mg. were dissolved in the petroleum ether and were presumed to be lipid. On a wet-weight basis the liver contained 6 per cent fat.

petroleum ether was 25 per cent of the dry weight or 6 per cent of the wet weight. Glycogen was 3.3 per cent of the wet weight. These were considered to be normal values.

The remainder of the biopsy was examined microscopically. There was considerable alteration of the lobular pattern and the hepatic cells often were grouped in an alveolar or tubular pattern. While the majority of parenchymal cells did not contain excessive amounts of fat, many were distended by a single large lipid vacuole. There was evidence of stasis of bile. Focal cellular necrosis and early fibrotic changes were observed. The details of the histologic appearance of the liver will be described in a separate report.[12]

TABLE I. A COMPARISON OF THREE GALACTOSE TOLERANCE TESTS, TWO BEING PERFORMED PRIOR TO THERAPY AND ONE AFTER THERAPY*

1. TOTAL BLOOD SUGAR IN MG. PER CENT

	BEFORE TREATMENT		AFTER TREATMENT
Date (1949)	Jan. 18	Jan. 24	Mar. 17
Fasting	133	132	200
15 minutes	207	253	400
45	200	228	338
75	190	204	278
105	198†	192	216
135	217†	152	256

2. FRACTIONATION OF BLOOD SUGARS

	A. GLUCOSE BLOOD LEVEL IN MG. PER CENT (FERMENTABLE REDUCING SUBSTANCES)			B. GALACTOSE BLOOD LEVEL IN MG. PER CENT (NONFERMENTABLE REDUCING SUBSTANCES)		
	BEFORE TREATMENT		AFTER TREATMENT	BEFORE TREATMENT		AFTER TREATMENT
Date (1949)	Jan. 18	Jan. 24	Mar. 17	Jan. 18	Jan. 24	Mar. 17
Fasting	31	58	14	102	74	186
15 minutes	60	117	68	147	136	332
45	54	99	32	146	129	296
75	50	74	44	140	130	234
105	79†	63	20	119†	129	196
135	101†	32	80	116†	120	176

3. RETENTION OF GALACTOSE IN BLOOD AFTER INTRAVENOUS INJECTION (RISE OF NONFERMENTABLE REDUCING SUBSTANCES ABOVE THE FASTING LEVEL)

	BEFORE TREATMENT		AFTER TREATMENT
Date (1949)	Jan. 18	Jan. 24	Mar. 17
Fasting	0	0	0
15 minutes	45	62	146
45	44	55	112
75	38	54	48
105	17†	55	10
135	14†	46	Minus 10

*In the first test, 0.5 Gm. per kilogram, and in the subsequent two tests, 1.2 Gm. per kilogram body weight of galactose were given intravenously (micromethod).

†In the first test (Jan. 18, 1949), 0.2 c.c. of epinephrine was administered subcutaneously at 75 minutes. Therefore, the 105- and 135-minute specimens marked with a dagger represent the response of the blood sugars to epinephrine.

TABLE II. INTRAVENOUS GLUCOSE TOLERANCE TEST
(0.5 GM. PER KILOGRAM BODY WEIGHT)

TIME	BLOOD GLUCOSE IN MG. PER CENT
Fasting	121
2 minutes	235
5 minutes	215
15 minutes	206
20 minutes	159
30 minutes	137

The patient's postoperative course was uneventful. His urine remained free of both sugar and albumin while he continued on the Nutramigen formula. At the time of discharge from the hospital he weighed 4,000 grams, a gain of 640 grams over his weight just prior to the change in formula.

On return home from the University of California Hospital his weight was 4,300 grams and his length was 57 cm. The liver was still enlarged to 6 cm. below the costal margin. The spleen was felt 2.5 cm. below the left costal margin. The biopsy scar was well healed. He was kept on a Nutramigen formula, but because of failure to gain weight was given banana flakes in addition.

Three weeks later he returned to the University of California Hospital weighing 5,300 grams. He appeared to be well developed, well nourished, and vigorous. The liver had decreased in size and was palpable to 2.5 cm. below the right costal margin. The spleen was barely palpable. Examination otherwise gave normal findings. At this time the icterus index was 7 units, thymol turbidity 1 unit, and the cephalin flocculation test was negative. Total serum protein was 4.8 Gm. per cent. The serum albumin was 4.1 Gm. per cent and the globulin was 0.7 Gm. per cent. The Bromsulphalein test showed 2 per cent retention in 60 minutes (Table III). The urine was normal. The intravenous galactose tolerance test was repeated (Table I). This demonstrated improvement in ability to metabolize galactose, but there was still a marked intolerance compared to normal. Since the tolerance tests had been done by the micromethod in the Pediatric Laboratory, one galactose tolerance test using the macromethod was done. The Hospital Clinical Laboratory obtained results shown in Fig. 2. The level of 125 mg. per cent at 75 minutes is an exceptionally high figure and demonstrated beyond doubt the specific diminished ability of this patient to metabolize galactose.

TABLE III. BLOOD CHEMISTRY AND HEPATIC FUNCTION TESTS

TEST	BEFORE TREATMENT (JAN., 1949)	AFTER TREATMENT (MARCH, 1949)
Thymol turbidity (units)	5	1
Cephalin flocculation	1 plus	Negative
Icteric index (units	17	7
Total proteins (Gm. per cent)	5.6	4.8
Albumin (Gm. per cent)	3.7	4.1
Globulin (Gm. per cent)	1.9	0.7
Bromsulphalein	Less than 1 per cent after 30 minutes	2 per cent after 60 minutes
Nonprotein nitrogen (mg. per cent)	35	———
Cholesterol (mg. per cent)	95	———

During this entry a milk diet was resumed, but within twenty-four hours galactosuria recurred. This once again cleared promptly upon return to a lactose-free regimen.

At 7 months of age the infant weighed 8.4 kilograms and was 71 cm. in length. He had four teeth and sat up alone. He had had one attack of pharyngitis with a fever of 39.0° C. which responded promptly to an injection of 300,000 units of Duracillin. His diet has been the same as that of any normal 7-month-old infant, with the exclusion of milk and milk products. The urine has been examined each month and has remained free of sugar and albumin. There has been no evidence of cataract formation or of mental retardation.

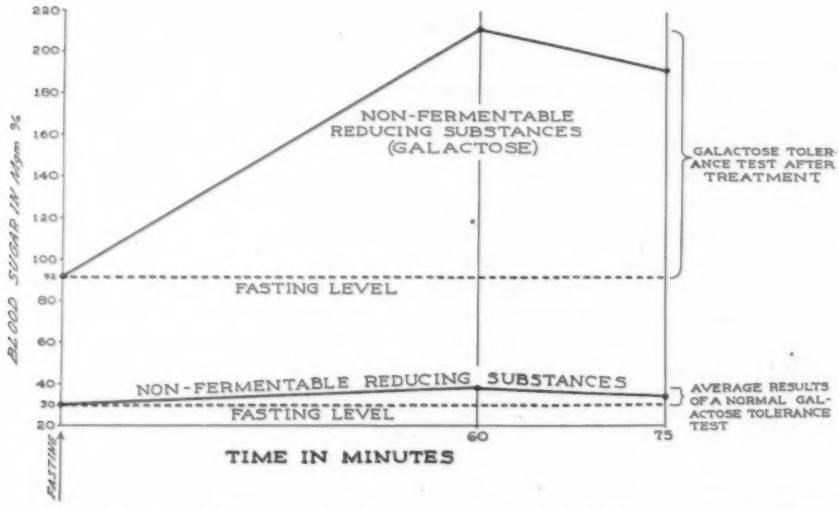

Fig. 2.—Intravenous galactose tolerance tests. A comparison of a normal galactose tolerance curve with that demonstrating the marked galactose intolerance present in Case 2. The test was performed after treatment started, with 0.5 Gm. per kilogram body weight of galactose given intravenously. The distance above the upper dotted line represents the amount of galactose retained in the blood after its intravenous injection. In a normal individual all or nearly all of this retained galactose would be removed within a seventy-five minute period (macromethod).

COMMENT

It has been generally agreed that galactosemia represents a congenital metabolic disorder in which the tissues are unable to metabolize galactose normally. That this syndrome is a congenital familial process has been shown by the early report of Göppert,[2] who described four siblings with the characteristic clinical manifestations of the disease.

Enlargement of the liver and evidence of hepatic functional impairment have been consistent features of the process. Mason and Andersen[13] included galactosemia as a form of von Gierke's or glycogen-storage disease. These authors believed that the high blood level of galactose was associated with excessive hepatic conversion of glucose to glycogen, thus resulting in depression of the

blood glucose by excessive storage of hepatic glycogen. Norman and Fashena[6] agreed with this view but also suggested that the reversible hepatomegaly in these cases might be due to the storage of some other substance within the liver such as fat or even galactose itself. They felt that the hepatic storage of lipid appeared unlikely in view of the normal blood values for cholesterol and lipid phosphorus found. Mellinkoff and his co-workers[7] also questioned the hypothesis of Mason and Andersen since in glycogen-storage disease there is little evidence of hepatic dysfunction. They proposed that galactose itself (or a polymer) was stored in the liver and was responsible for the hepatic injury. It was found that after ingestion of 3.5 Gm. of galactose by their patient, only traces of this substance were found in the urine, suggesting to these authors that most of the galactose was either converted to glucose in the liver or stored there.

The histologic pattern in the liver in glycogen storage disease is well known. The hepatic cells are enlarged and contain excessive amounts of glycogen. These altered cells have been described as "plant-like."[14] In the two incomplete pathologic descriptions of the liver in galactosemia,[1, 15] the characteristic hepatic lesions of glycogen disease were not present. Cirrhosis was described in one instance.[1] In the other the recorded description was limited to an abnormal acinar grouping of the hepatic cells.[15]

In the two cases in patients presented in this paper the hepatic alteration consisted mainly of fatty infiltration. While increased amounts of hepatic fat is one of the characteristics of glycogen-storage disease, the amount of fat is exceeded greatly by the stored glycogen. The fatty livers in these siblings, particularly in the one dying at 8 days of age, closely resemble the fatty livers found in patients with diabetes or alcoholism, or those produced experimentally by high fat diets or other means.[16, 17] They had no resemblances to the livers of patients with glycogenosis.

Although the diagnosis of galactosemia was not made in the first infant who died at the age of 8 days, that infant's clinical course was identical with the pretreatment course of the second sibling. Since the disease had been described previously in siblings,[2] it may be safely assumed that both infants were suffering from the same disease process, and that the differences in the structure in the two livers were the result of treatment by withdrawal of galactose from the diet of the second infant.

Characteristically, infants with galactosemia appear to be normal at birth and for a few days thereafter. There is no icterus, hepatic enlargement, or signs of portal obstruction until milk has been ingested for a period of several days. It seems apparent that there may be a quantitative variation in the severity of the defect of galactose metabolism. With complete or nearly complete inability to metabolize galactose, death may occur only a few days after birth, as in our first patient. Other children with this disease apparently can metabolize some galactose. Although they may survive, they are generally severely malnourished by the time they are 2 or 3 months of age. In some instances intolerance to galactose diminishes after several years.[2, 5]

Most of these infants with galactosemia have had brief periods of icterus in the early weeks of life with none thereafter. Although usually coinciding with the time of physiological jaundice of the newborn infant, in one patient icterus persisted for the first eight months of life.[2]

While the relationship of ingestion or withdrawal of galactose to the appearance or disappearance of the clinical and laboratory signs seems consistent, the possibility of the milk-free diet causing amelioration of the hepatic disease in part by a lipotropic action must be considered, since in the more recently reported cases the milk-free diet has consisted in part of amino acid mixtures containing methionine. The characteristic clinical sequences strongly suggest that the fatty infiltration of the liver occurs secondarily to the disordered utilization of galactose.

It is possible that the inability to metabolize galactose normally with the resulting fatty liver is comparable to the situation in poorly controlled human or experimental diabetes where abnormal metabolism of glucose is often associated, for reasons yet unknown, with fatty infiltration of the liver. When insulin is withheld from the depancreatized dog, extensive fatty infiltration of the liver occurs within seventy-two hours.[18] It would appear that hepatic infiltration with fat may occur in galactose diabetes almost as rapidly.

Distention of the hepatic cells with fat may have two secondary effects: First, it can produce (1) intrahepatic biliary obstruction with jaundice; (2) intrahepatic portal venous obstruction with ascites, splenomegaly, and abdominal venous distention; and (3) degeneration or necrosis of hepatic cells with scarring or cirrhosis. Second, the lipid infiltration of the liver interferes with hepatic function as evidenced by positive cephalin flocculation and thymol turbidity tests, retention of Bromsulphalein, and lowering of the plasma proteins and prothrombin. It is probable that if the intolerance to galactose were not complete, the inability of the liver to metabolize the substance would be accentuated when hepatic function was diminished by the infiltration of fat. In other words, once the liver becomes fatty the galactosemia and galactosuria may be secondary reactions in part. That this may occur is suggested by the findings in the case of Mellinkoff and his co-workers,[7] in which, after the signs of hepatic disease were disappearing, ten days after galactose had been excluded from the diet, ingestion of galactose was followed by excretion of only traces of the substance. In our Case 2, a galactose tolerance test indicated increased tolerance to the carbohydrate after milk had been eliminated from the diet (Table I). Some evidence of improvement of hepatic function was also shown to occur (Table III). The fact that the severity of intolerance to galactose in this disease may vary, depending upon the degree of fatty infiltration of the liver, is consistent with a new concept we are proposing in the pathogenesis of galactosemia.

The fatty infiltration of the liver observed in these infants is identical with the pathologic pattern seen in diabetes, alcoholism, and in fatty livers produced experimentally in animals by a variety of methods. That cirrhosis eventually may follow this infiltration with fat is well known.[16, 17] If the hepatic infiltration

of fat in galactose diabetes persisted, significant cirrhotic changes should undoubtedly occur. In the first report of this syndrome Von Reuss[1] described a cirrhotic liver resembling that of chronic alcoholism.

The results of the carbohydrate tolerance tests performed on our patient (Case 2) of this paper are summarized in the accompanying figures and tables. In Table I are the comparative results of galactose tolerance tests done before and after the institution of therapy. In all tests an extraordinarily high fasting level of nonfermentable reducing substance, presumably chiefly galactose, was found. The fasting level of fermentable reducing substance, glucose, was low in all tests. Fifteen minutes following the intravenous injection of galactose there was an elevation of the level of total blood sugar and of both of its fermentable and nonfermentable fractions. During the next hour the total blood sugar and its fractions dropped slightly. Marked impairment of galactose metabolism is shown by the high fasting level of galactose and the prolonged galactose retention in the blood after intravenous injection. This fact was also clearly shown in the galactose tolerance test outlined in Fig. 2.

Comparative results of the galactose tolerance tests done before and after therapy were interpreted as indicating increased tolerance to galactose at the time of the later test. Although the galactose level rose higher after intravenous injection, during the later test it fell more rapidly than it had before, and after 105 minutes had elapsed nearly all the injected galactose had been removed from the blood (Table I, part 3). The retention of 48 mg. per cent of galactose at seventy-five minutes indicated that pronounced impairment of galactose metabolism was still present.

The prompt rise of the level of blood glucose following the injection of epinephrine demonstrated that glycogenolysis does occur normally in these patients. The fall of the level of galactose during the rise of the glucose level (after the injection of epinephrine) and the presence of a high fasting level of nonfermentable reducing substance (galactose) with a very low level of fermentable reducing substance (glucose) confirms in part the reciprocal relationship between galactose and glucose levels which had been observed previously in *oral* galactose tolerance tests.[8, 19] However, in our patient (Case 2) this same relationship was not observed following the *intravenous* injection of galactose since both glucose and galactose rose simultaneously (Fig. 1). Why the glucose level rose following the intravenous injection of galactose when it falls following oral administration of galactose[8] remains unexplained.

It is apparent that galactemia interferes in some unknown way with normal metabolism of glucose. Goldbloom and Brickman[9] have suggested that there may be interference with and diminution of absorption of glucose through the intestinal mucosa by simultaneous absorption of galactose and by the high total blood sugar. Bruck and Rapoport[8] believed that glucose and galactose competed in a common metabolic mechanism, probably in the liver. As evidenced by a normal intravenous glucose tolerance curve in our Case 2 (Table II), there seems to be no interference with glucose metabolism per se in this disorder.

The question of why this metabolic defect has such a profound effect on the entire body led Mason and Turner[5] to postulate that the low blood glucose levels

resulted in a relative starvation of all the tissues and thus impaired the function of their cells. Bruck and Rapoport[8] and Mellinkoff and his co-workers[7] have pointed out, however, that hypoglycemia from other causes, such as von Gierke's disease or hyperinsulinism, does not result in similar symptoms or in hepatic or renal damage. It has been noted by most observers that during galactose tolerance tests, despite very low blood glucose levels obtained, hypoglycemic shock usually does not occur as long as the blood galactose level remains high.

Bruck and Rapoport[8] found that the galactose level in the spinal fluid is equal to that in the blood stream and felt, therefore, that galactose probably freely diffuses into all the body tissues and fluids. They postulated that the severe manifestations of this disease were toxic in nature and resulted from prolonged high blood galactose levels. Mitchell and Dodge[20] first indicated the toxic nature of galactose on body tissues when they found that all rats fed on a ration containing 70 per cent galactose developed cataracts. These same authors demonstrated that these cataracts were reversible if treated early by placing the animal on a diet free from lactose. A number of reports have appeared indicating the inadequacy of lactose as a dietary carbohydrate in the rat.[21, 22]

It is apparent from the cases reported to date that early diagnosis and prompt institution of appropriate treatment offer these children a good prognosis, since the early pathologic manifestations of the disease are reversible. Those infants having severe impairment of galactose metabolism will die early in life unless a prompt diagnosis is made. Those with less impairment of galactose utilization may survive for longer periods. If treatment is instituted late, irreversible changes will develop. These include cataracts, severe malnutrition, hepatic damage, or cirrhosis, and mental deficiency.

Treatment of this disease consists of a lactose-free diet with the employment of a milk substitute such as Nutramigen or a soy bean formula. Recent work of Greenman and Rathbun[11] suggests that a diet high in carbohydrate is also important, for it has been shown experimentally to improve the galactose tolerance. Thus the effects of small amounts of galactose unavoidably included in the patient's diet may be minimized. In view of the excessive hepatic fat, choline might also be included in the diet.

SUMMARY

1. The literature of galactose diabetes has been reviewed with reference to the clinical manifestations, the disordered metabolism of carbohydrates, and the pathologic lesions in fourteen cases which have been recorded previously.

2. Two cases of galactose diabetes in siblings are herein reported. In the first infant death occurred at the age of 8 days. The second infant had an identical early clinical course with icterus and hepatomegaly. Following the demonstration of galactemia and galactosuria, elimination of lactose from the diet caused reversal of all clinical and laboratory signs of the syndrome.

3. Fatty infiltration of the liver was demonstrated in both infants. Less fat was observed in the liver of the second sibling, but early cirrhosis had already occurred.

4. It is proposed that infiltration with fat rather than glycogen is the basic cause of the hepatic enlargement and dysfunction in this disease. Furthermore, there is evidence that excessive fat in the hepatic cells may accentuate the congenital inability of the liver to metabolize galactose normally.

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TYPHOID FEVER IN FOURTEEN CHILDREN TREATED WITH CHLORAMPHENICOL

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SINCE the original work by Woodward, Smadel, and associates[1] on the treatment of typhoid fever with chloramphenicol, there have been several reports from various parts of the country on its efficaciousness.[2, 3] Our first cases were treated in March, 1949. In the interval from March until the present date, Oct. 1, 1949, we have treated a total of nine children with chloramphenicol (Chloromycetin), all of whom showed rapid response to the drug. All of our cases were proved by suspicious clinical course, positive blood, stool, and urine cultures, and by diagnostic blood agglutinin titers.

The ages of our patients varied from 2½ to 13 years; there were six girls and three boys, seven of whom were white and two Negro. Two of the patients had a history of previous immunization for typhoid within the previous year.

Dosage of the Drug and Patients' Responses.—The treatment was begun from eight to thirty-four days (average, fifteen and one-quarter days) after onset of disease. We could not correlate the length of the illness before Chloromycetin was started with the length of time when response to the drug took place.

All of our patients were treated with initial dosage of 50 mg. per kilogram of the body weight followed by 125 mg. irrespective of weight every two to three hours in the smaller children, and 250 mg. every two to three hours in the larger children for approximately six days; then the dosage was given every four to six hours. The total dosage varied from 8 Gm. to 29 Gm. with total dosage averaging 13 Gm. The oral ingestion of the drug was not difficult. It can be given rectally in a 25 to 50 per cent greater dose; the capsule tip can be perforated for ease and quickness of absorption. Suppositories will be available. It can be used intravenously as a 10 per cent propylene glycol solution.

The number of hours before the patient was fever-free varied from forty-eight to ninety-six hours, with a rough average of seventy-two hours.

Between March and October, 1949, we did not withdraw the drug until there was a period of from four to five days of normal temperature (a total of seven to nine days of such therapy). Since mid-September, in line with the experience of Smadel and associates,[4] we gave the drug for eight to fourteen days to two of the nine patients to prevent relapse.

COMMENT

As with all specific therapies, we were concerned early in these trials with ultimate immunity, both its degree and duration. If one stops typhoid early in its course, will the patient have sufficient immunity to protect against subsequent exposure? This is important in any area where typhoid risks are prevalent.

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TABLE I

CASE NO.	AGE (YR.) SEX RACE	IMMUNIZATION	LABORATORY EXAMINATION	DAY OF DISEASE WHEN CHLOROMYCETIN STARTED	THERAPY: TOTAL CHLOROMYCETIN (GM.)	THERAPY: NO. OF DAYS OF TREATMENT	DURATION OF FEVER AFTER CHLOROMYCETIN STARTED (HOURS)	RELAPSE CARRIER
1	3 F W	No	Positive blood and stool culture	14	15	8	48	
2	2½ F W	No	Positive blood and stool culture Agg. O 1:320 H 1:320	34	10	13	60	
3	13 F N	Completed 9 months before	Agg. O 1:640 H 1:640	12	29	12	96	Fever again 14 days after discharge. Not examined or treated. Stool culture negative on two different exams.
4	5 F W	No	Positive stool and urine culture Agg. O 1:640 H 1:1280	21	8	4	48	
5	7 F W	No	Positive blood culture Agg. O 1:640 H 1:2560	10 28	13 13	6 7	96 48	Relapse 8 days after stopping Chloromycetin
6	11 M W	No	Agg. O 1:320 H 1:640	12	13	5	72	
7	5 M W	No	Agg. O 1:320 H 1:640	14	11	10	72	
8	8 M W	No	Agg. O 1:160 H 1:320	14	11	10	96	
9	13 F N	Completed 4 months before	Positive blood, stool, and urine cultures Agg. O 1:1280 H 1:640	8	15	14	72	

Apparently our patients, as judged by the agglutinins, are protected to some satisfactory degree. Follow-up has verified this. The short duration of the disease before giving Chloromycetin (an average of thirteen and one-third days) was sufficient to generate adequate agglutinin levels. At least for the immediate future, they are probably sufficiently protected through having had typhoid for so short a time. The crucial test will be future check-ups by Widal levels and possible re-exposure. One must bear in mind that other than agglutinin antibodies, which these patients may have formed, are involved in immunity; we did not have facilities for such tests.

All cases had negative excreta on two occasions, five days apart, usually starting five days after Chloromycetin was stopped. Stool examinations once or twice at one to two months after being at home have not revealed a carrier. Future check-ups will be done to be sure of carrier state. A single mailed stool, which is negative, is not sufficient proof to rule out a carrier.

A relapse case (patient B. M.) had six days of this therapy; this was too little therapy; she relapsed eight days later; then seven additional days of therapy completely eradicated the disease. Another patient (C. L.) probably had a relapse as nearly as could be judged by the recurrence of fever for two weeks at home, just after leaving our hospital; she was not attended by a physician nor treated at her home, but we did not learn of this until some weeks after this occurrence. However, it was noted that stools were negative twice subsequently. We observed another relapse in an adult (not included in this group) when she could not be treated for more than four days.

SUMMARY

Nine children with typhoid have been cured with chloramphenicol in an initial dose of 50 mg. per kilogram followed by 125 to 250 mg. single doses every two to three hours until fever first disappeared, an average of about two to four days, and then every four to six hours during four to five days of normal temperature. Two relapses occurred which the drug quickly stopped. There were no drug reactions, disease complications, sequelae, or known carriers.

At the time of submitting this paper for publication, Feb. 22, 1950, five additional cases of typhoid have been similarly treated successfully; follow-up showed patients to be the same as stated in summary.

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AUREOMYCIN TREATMENT OF PERTUSSIS

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THE antimicrobial spectrum of aureomycin activity embraces a larger number of the causative agents of severe, acute respiratory tract infections than that of either of its most useful and effective predecessors among the antibiotics, namely, penicillin and streptomycin. Furthermore, aureomycin is effective when given by mouth and is relatively free of toxic effects. It, therefore, was deemed worthy of extensive clinical trials in all types of serious respiratory-tract infections. Numerous reports of its successful use in various bacterial pneumonias,[1-6] primary atypical pneumonia,[7-10] miscellaneous bronchopulmonary infections,[11-14] psittacosis,[15] and Q-fever[15, 16] have already appeared. A preliminary clinical trial in pertussis reported by Bell, Pittman, and Olson[17] suggested that aureomycin shortened the clinical course of this disease in patients treated in their homes when compared with untreated patients observed in previous years in the same community. The present report deals with the effects of oral aureomycin on the clinical course and bacteriologic findings in twenty-two hospitalized patients when compared with a similar number of comparable and contemporary patients treated on the same hospital ward without the benefit of any antibiotic therapy.

PLAN OF INVESTIGATION

Selection of Cases.—The patients included in this study were all observed on the same ward in the South Department of the Boston City Hospital during the four months, August through November, 1949. All had clinical findings consistent with pertussis but they were admitted to the series only after *Hemophilus pertussis* was identified in their nasopharyngeal culture. Several of the patients were admitted to the hospital during the catarrhal or early paroxysmal stage only after a bacteriologic diagnosis was established from cultures made because they had been exposed to other patients who were previously admitted with fully developed whooping cough. Strict alternation of patients for aureomycin therapy was not observed in this preliminary study, treatment being given or withheld from patients in small groups for convenience, but no conscious selection was employed.

Clinical Data.—A careful history was obtained in each case, with a special effort being made to determine the date of onset of catarrhal symptoms and whether or not the patient had received pertussis immunization. The ward to

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which these patients were admitted had at least one nurse in constant attendance who charted the number and severity of paroxysms of cough.* The severity of the paroxysms was arbitrarily classified as mild, moderate, or severe at the time they were observed by the attending nurse.

Laboratory Data.—Nasopharyngeal cultures were made according to the method recommended by Bradford, Day, and Berry[18] at the time of admission and at intervals thereafter. The organisms were identified by their colonial and microscopic morphology and by slide agglutination with specific rabbit antiserum. Total and differential leucocyte counts were taken at least once each week. Roentgenograms of the chest were taken only when indicated.

Aureomycin Therapy.†—The dose of aureomycin used in the first 10 patients was about 100 mg. of the crystalline hydrochloride per kilogram body weight per day, and subsequent patients were given 60 mg. per kilogram per day. Treatment with aureomycin was continued for a total of five days in the first 10 patients and because of inadequate bacteriologic and clinical responses in 3 of these 10 patients, subsequent patients were treated for ten days. Two of the 3 patients who relapsed were given a second course of aureomycin for five days. The daily amount was divided into four equal doses and was given during feedings, the contents of the capsules being mixed with apple sauce or some other aceptable vehicle or incorporated in a small portion of the formula which was given first and then promptly followed by the remainder of the formula. If vomiting occurred less than an hour after a dose, the same dose was promptly repeated. The patients who did not receive aureomycin were not given any antimicrobial agents except for the treatment of complications, and no antiserums were used in any of the patients.

ANALYSIS OF CASES

A total of 22 patients were treated with aureomycin and a similar number were observed without antibiotic therapy during the same four-month period. The distribution of patients in the two groups according to age, history of previous immunization, and duration of catarrhal symptoms prior to admission is shown in Table I. The two groups were quite comparable with respect to the age distribution. Among the aureomycin-treated patients, 6 had received pertussis immunization prior to the onset of this illness, 2 of them had been incompletely immunized within two months, and the other 4 had been vaccinated more than one and one-half years previously. Among those who received no antibiotic therapy, a definite history of pertussis immunization was elicited in 4 patients while in 4 others the history of such immunization was not known. The average duration of symptoms at the time of admission to the hospital was about the same in the two groups, but the delay in beginning aureomycin administration ranged from one to eight days and averaged almost four days. Other features such as number and severity of paroxysms and occurrence of leucocytosis during the first three or four days in the hospital were also very similar in both groups of patients.

*We are indebted to Mrs. Mary M. Perez, R.N. for assistance in this study.

†The aureomycin hydrochloride was provided in capsules of 50 and 250 mg. each by the Lederle Laboratories.

TABLE I. ANALYSIS OF CASES (TWENTY-TWO PATIENTS)

ANTIBACTERIAL THERAPY:	AUREOMYCIN	NONE
Number of Patients	*22*	*22*
Age: 6 months or less	6	7
7-12 months	3	5
1-3 years	8	7
More than 3 years	5	3
Pertussis Immunization:		
Yes	6	4
No	16	14
Unknown	0	4
Duration of Cough Before Admission to Hospital:		
7 days or less	9	7
8-10 days	6 (10)*	6
11-15 days	7 (7)*	9
16-20 days	(5)*	
Average	8.8 (12.5)* days	9.5 days

*Figures in parentheses based on duration of cough to time aureomycin was begun.

CLINICAL RESULTS

Effect on Cough.—The frequency and intensity of the paroxysmal cough began to decrease after the second or third day of aureomycin therapy and, in most of the aureomycin-treated patients this decrease in symptoms continued steadily until the cough subsided completely and the patients were discharged. In 3 of the 10 patients who received aureomycin for only five days there was a relapse in symptoms within the first few days after the antibiotic treatment was stopped and in 2 of these 3 patients the paroxysms were again brought under control after a second course of aureomycin given for five days. Among the 12 patients who were treated with aureomycin for ten days, 2 had an increase in cough for several days after apparent improvement. Most of the patients who did not receive any aureomycin had little or no change in the cough, which continued with the same intensity and in some patients even became aggravated during the first two weeks in the hospital and then gradually began to improve.

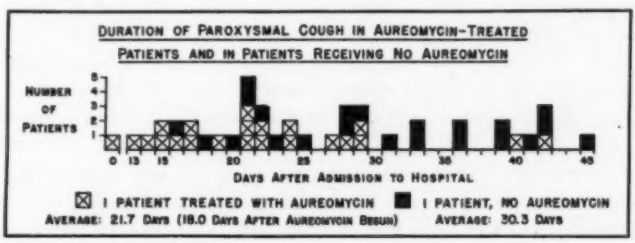
DURATION OF PAROXYSMAL COUGH IN AUREOMYCIN-TREATED PATIENTS AND IN PATIENTS RECEIVING NO AUREOMYCIN
NUMBER OF PATIENTS
0 13 15 20 25 30 35 40 45
DAYS AFTER ADMISSION TO HOSPITAL
1 PATIENT TREATED WITH AUREOMYCIN
1 PATIENT, NO AUREOMYCIN
AVERAGE: 21.7 DAYS (18.0 DAYS AFTER AUREOMYCIN BEGUN)
AVERAGE: 30.3 DAYS

Fig. 1.

Duration of Cough.—The total duration of the paroxysmal cough for the individual cases in both groups is shown in Fig. 1 and the data for each of the two groups of patients are summarized in Table II. The average duration of the paroxysmal cough in the hospital was about eight and one-half days shorter among the patients who were treated with aureomycin than in those

who were not so treated. The total duration of the paroxysms in the latter cases was 30.3 days after admission to the hospital while in those treated with aureomycin the paroxysms continued for an average of 21.7 days after admission or eighteen days after the first dose of aureomycin.

TABLE II. DURATION OF PAROXYSMAL COUGH

THERAPY	NUMBER OF PATIENTS HAVING PAROXYMS OF COUGH IN THE HOSPITAL FOR:			AVERAGE DURATION OF PAROXYSMS (DAYS)
	19 DAYS OR LESS	20-29 DAYS	30 DAYS OR MORE	
Aureomycin	9 (15)*	11 (5)*	2 (2)*	21.7 (18.0)*
No aureomycin	2	9	11	30.3

*Figures in parentheses based on number of days after aureomycin therapy was started.

Frequency of Paroxysms.—An analysis of the cough charts as recorded at the beside shows more clearly the favorable effect of aureomycin on the number and severity of the paroxysms. The average numbers of paroxysms in all of the patients in each group, including the apparent treatment failures, are charted for each day in the upper panel of Fig. 2. For the patients who received aureomycin the average number of paroxysms dropped sharply and steadily from the seventh to the fourteenth days, leveled off for the next five days, and then continued downward more slowly. The level portion of the curve is due to the five patients who relapsed following therapy. By contrast, the first drop in the average number of paroxysms per day among the patients who were not given aureomycin occurred on the seventeenth hospital day and the decline then continued steadily.

Cough Index.—In order to assess the severity as well as the frequency of paroxysms, a "cough index" was established. For this purpose the following arbitrary ratings were assigned to each paroxysm according to the severity, as recorded by the attending nurses: severe—4; moderate—2; and mild—1. The total of these values for each day was termed the cough index. The charts of the average daily cough index for the 22 aureomycin-treated patients and for the group of patients who did not receive aureomycin are shown in the lower panel in Fig. 2. These two curves are very similar to those which appear in the upper panel of the same figure except for the more precipitate character of the initial drop in the cough-index curve representing the aureomycin-treated patients.

Leucocyte Counts.—There did not appear to be any correlation between the total or differential blood counts and the progress or severity of the disease in the present cases. This was true both among those treated with aureomycin and in those from whom this antibiotic was withheld. After the second hospital week, however, the total counts were significantly lower in the aureomycin-treated cases.

Mortality and Complications.—There were no fatalities in either group. Only one complication, namely, otitis media, occurred in one of the patients who did not receive aureomycin, and this was the only patient in both groups who had any significant fever.

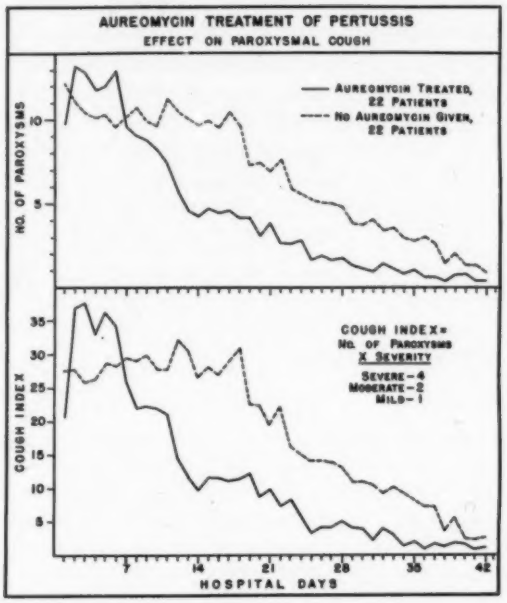
AUREOMYCIN TREATMENT OF PERTUSSIS
EFFECT ON PAROXYSMAL COUGH
AUREOMYCIN TREATED, 22 PATIENTS
NO AUREOMYCIN GIVEN, 22 PATIENTS
NO. OF PAROXYSMS
COUGH INDEX
COUGH INDEX = NO. OF PAROXYSMS X SEVERITY
SEVERE – 4
MODERATE – 2
MILD – 1
HOSPITAL DAYS

Fig. 2.

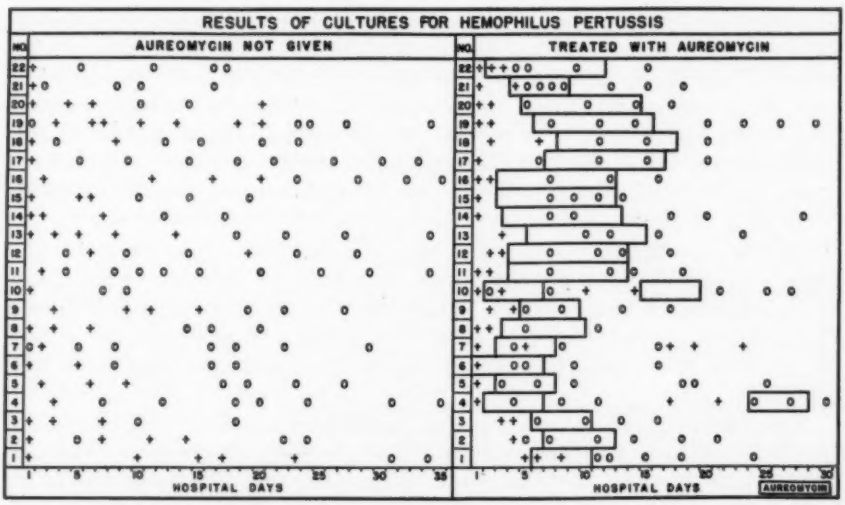
RESULTS OF CULTURES FOR HEMOPHILUS PERTUSSIS
AUREOMYCIN NOT GIVEN
TREATED WITH AUREOMYCIN
NO.
HOSPITAL DAYS
AUREOMYCIN

Fig. 3.

BACTERIOLOGICAL RESULTS

The results of the nasopharyngeal cultures for *H. pertussis* are shown in Fig. 3. As already noted, the first 10 aureomycin-treated patients received the antibiotic for only five days; among these 10 patients, 3 had a bacteriologic relapse. They were the 3 patients who also had clinical relapses. The last positive cultures in these patients were obtained on the twenty-first, twenty-third, and fourteenth hospital days. In all the other patients who were treated with aureomycin all the cultures taken after the third day of therapy were negative for *H. pertussis*. Among the 22 patients who did not receive aureomycin, there were 12 who had positive cultures on or after the seventh day in the hospital and 7 had positive cultures on or after the 14th hospital day. The last positive culture in all the patients who did not receive aureomycin was obtained on an average of nine days after admission.

TOXICITY

There were 6 patients who had loose bowel movements and some vomiting unrelated to paroxysmal coughing during the period of aureomycin treatment. In no instance was this severe enough to warrant discontinuing the therapy. There were no other toxic effects of aureomycin noted in any of the patients.

DISCUSSION

Reports on the effects of streptomycin on pertussis have been conflicting. Thus, Gordon, and Almaden[19] recorded definite and rapid improvement and a significant reduction in mortality in 24 patients with severe pertussis treated with streptomycin. Leichenger and Schultz[20] also observed a reduction in the number of paroxysms in two groups of 8 patients each, one of them treated with intramuscular streptomycin and the other group given the same antibiotic by aerosol. They found the latter route to be the more effective one. On the other hand, Schwabacher, Wilkinson, and Karran[21] treated 17 patients with pertussis with streptomycin, mostly by aerosol, and in none of them, whether in the catarrhal, early paroxysmal, or advanced stage, was the streptomycin beneficial in spite of the fact that the organisms were found to be sensitive to the antibiotic in vitro.

Similar conflicting results have been recorded for polymyxin B in pertussis. Swift[22] observed a definite response within the first forty-eight hours of treatment with this agent in 10 unselected cases. Kaplan, Fischer, and Kohn,[23] on the contrary, found no effect in 84 patients with pertussis whom they treated with this agent, irrespective of the stage when the treatment was started.

The observations presented in this paper confirm the beneficial clinical effects of aureomycin in pertussis reported by Bell, Pittman, and Olson.[17] The number, severity, and duration of paroxysms were significantly reduced in the aureomycin-treated patients as compared with concurrent cases of patients treated under the same conditions without antibiotics or antiserums. In the great majority, improvement began within the first three days of

therapy and continued steadily. Furthermore, when the aureomycin was given over a period of ten days, cultures from the nasopharynx became negative for *H. pertussis* after two or three days and the organisms could no longer be recovered from such cultures.

The possibility has not been entirely excluded that the effects observed were due to the influence of the antibiotic on secondary invaders which may give rise to mild and protracted irritation in the respiratory tract and which, in turn, prolongs the symptoms. The absence of fever or definite evidence of other upper-respiratory or pulmonary infection even in the patients who did not receive aureomycin, does not necessarily eliminate this possibility, although it renders it less likely.

These observations suggest that aureomycin is a useful agent in pertussis and deserves more extended clinical trials.* The present study is, therefore, being continued with modifications in the choice of cases, and it is hoped also to have an opportunity to evaluate some other promising antibiotic agents in this disease.

SUMMARY AND CONCLUSIONS

Aureomycin was used orally in the treatment of 22 hospitalized patients with pertussis and the clinical and bacteriologic findings in these patients were compared with those in a similar number of comparable and contemporary patients treated under the same conditions without any antibacterial therapy. Improvement began soon after aureomycin treatment was started and continued steadily in 17 of the patients. The number, severity, and duration of paroxysms were significantly reduced in the aureomycin-treated patients.

Nasopharyngeal cultures became negative for *H. pertussis* soon after aureomycin was started and this organism could then no longer be obtained in such cultures from any of the patients who were treated for ten days. Bacteriologic and clinical relapses occurred in 3 of 10 patients in whom aureomycin was given for only five days.

Toxic effects from aureomycin were limited to mild vomiting and loose bowel movements in a few patients, but this did not necessitate discontinuing treatment.

Aureomycin appears to be a beneficial agent in the treatment of pertussis.

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ELECTROENCEPHALOGRAPHIC FINDINGS IN ACUTE NEPHRITIS

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ONE of the hazards facing the child with acute nephritis is the development of symptoms referable to the central nervous system. These manifestations may consist of restlessness, dimness of vision, sudden blindness, diplopia, headache, drowsiness, vomiting, and severe convulsions possibly resulting in death. The frequency with which such symptoms develop is not fully established, but that they are common is well known.

There are two schools of thought as to the cause of these cerebral symptoms of acute nephritis: (1) constriction of arterioles in the brain producing anoxia of the cortex, and (2) cerebral edema. These two processes may coexist in the same patient. In rare instances, convulsions due to uremia may occur.

In order to determine the frequency of occurrence and the character of the cerebral dysfunction occurring in acute nephritis, we have employed the technique of electroencephalography. In twenty-four children with typical acute nephritis, 164 electroencephalograms (EEG) were obtained during the nephritic episode, and an attempt has been made to correlate the EEG findings with the clinical course. It is the purpose of this paper to present these findings.

METHODS EMPLOYED

Standard methods for assuring valid electroencephalograms were employed. The machine used was an Offner Type C 144 channel crystograph electroencephalograph. The EEG's were obtained in a special room near the nephritic ward. In addition to detailed clinical notes, blood pressure determinations were made immediately before and after the electroencephalographic tracings. Patients were wheeled the short distance down the hall to the EEG room, and every attempt was made to assure an atmosphere of calm, in order to prevent emotional tension which might cause an elevation in blood pressure.

Eight scalp electrodes were used as follows: two frontal, two precentral, two occipital, and two temporal. Electrodes were attached to each ear to be used as reference points. Separate scalp-to-ear runs were made from each of the eight scalp electrodes to the left ear reference electrode. Similar scalp-to-ear runs were made from each of the eight scalp electrodes to the right ear reference electrode. In a few cases, scalp-to-ear runs were made using the interconnected ear electrodes as a reference point. Initial scalp-to-scalp runs were made as follows: left frontal to left precentral, right frontal to right precentral, left precentral to left occipital, right precentral to right occipital. The second set of scalp-to-scalp runs were as follows: left frontal to left precentral, left precentral to left occipital, right frontal to right precentral, right precentral

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to right occipital. Triangulation techniques were employed on both sides as follows: frontal to precentral, precentral to occipital, occipital to temporal, temporal to frontal. Whenever an abnormality was noted in a particular area, more sensitive triangulation techniques were employed to localize more sharply the site of the abnormality.

Electroencephalograms were interpreted according to the Davis system.[1] In addition, alpha index was interpreted according to the scales set up by Lindsley[2, 3] and Bernhard and Skoglund[4] for children of various ages. This was done in order to differentiate waves in the slow frequency range commonly considered abnormal from those which are, in reality, normal for children of various age groups.

Standard methods for reducing hypertension in children with acute nephritis were employed. These included bed rest, barbiturate sedation, and the administration of magnesium sulfate. All of the patients were kept in bed. In the twenty-four hour period prior to taking the electroencephalographic tracings, twelve of the children received magnesium sulfate alone, and seven were given both magnesium sulfate and a barbiturate preparation, usually phenobarbital. The direct effects that these drugs might have on cortical electrical activity was taken into consideration in the interpretation of the tracings.

While there is lack of general agreement as to what constitutes hypertensive levels in children of various ages, we have considered systolic blood pressures in excess of 120 mm. of mercury as being beyond the normal range in children 2 years of age or over, and 110 mm. of mercury systolic as the upper limit of normal for children under 2 years of age. Blood pressure determinations were recorded repeatedly, attempts were made to eliminate emotional tension in the children, and cuffs of proper width were employed.

RESULTS OBTAINED

Of the twenty-four children with acute nephritis, twenty-two had abnormalities in the electroencephalogram at some time during the hospital stay. As the nephritis improved, the electroencephalograms tended to return to normal, although some of the patients were not followed long enough to determine whether or not the EEG's showed a complete return to a normal pattern of activity. We do not yet know if persistent abnormalities in the EEG can occur after acute nephritis.

Of the patients showing electroencephalographic abnormalities, the chief findings were:

1. Bursts of slow frequency waves of high microvoltage. The waves were in the range of 3 to 7 per second, and the amplitude ranged from 100 to 260 microvolts.

2. Instability of the electroencephalographic pattern characterized by lack of sustained rhythm, and marked irregularities evidenced by variations in amplitude and frequency.

3. Suppression of alpha activity associated with an increase in fast frequencies of 11 to 30 per second. However, when alpha activity did appear, the waves were of normal amplitude and frequency for children of the ages involved.

Figs. 1 to 5 illustrate the electroencephalograms obtained in children with acute nephritis.

These findings are very similar to those observed by Jost, Ruilmann, Hill, and Gulo[5, 6] in adult patients with hypertension but not having acute nephritis.

In the beginning of this work, it was thought that there might be a close relationship between the degree of hypertension and the nature of the EEG, as had been reported previously by Whitacre, Loeb, and Chin,[7] and by Jost[8] in obstetric patients with hypertension of eclampsia. However, in our studies on the electroencephalographic findings in acute nephritis, there was lacking the clear-cut correlation between hypertension and the character of the EEG which these observers noted in their patients. Some of the reasons may have been that our children with acute nephritis did not have the degree of hypertension encountered in the eclamptic group, the blood pressures were not reduced as precipitously, serial electroencephalograms were not obtained at such close intervals during the phase of falling pressure, and no electroencephalograms were made during or within a few hours of a convulsion associated with hypertension. Sudden reduction in hypertension of eclamptic patients was achieved by caudal analgesia in the majority of patients reported on by the above-mentioned authors. While caudal analgesia has been used to reduce hypertension in patients with acute nephritis,[9] no serial electroencephalograms have been obtained in such cases.

Not only was it impossible to correlate the electroencephalographic abnormalities with hypertension, but they also seemed to bear no clear relationship to edema, anemia, or azotemia. However, the number of patients with severe edema, marked anemia, or more than moderate azotemia was very small.

Variations from day to day were encountered in the serial EEG studies on these patients. Some of the children had abnormal electroencephalograms on admission to the hospital, while others only later had abnormal tracings. As the nephritis persisted, those children originally having normal electroencephalograms began showing definite EEG abnormalities, consisting of the appearance of slow waves of high microvoltage, instability of the tracing, and suppression of alpha activity with an increase of fast frequencies of low amplitude.

One of the most interesting patients was a 12-year-old boy who had sustained hypertension over a period of many days but whose serial electroencephalograms were within normal range except for one recording which was classified as borderline abnormal.

Inability to correlate blood pressure levels with electroencephalographic abnormalities is illustrated by the fact that some of the children admitted with hypertension had round normal electroencephalograms, but later, when the blood pressure was normal, the EEG was abnormal.

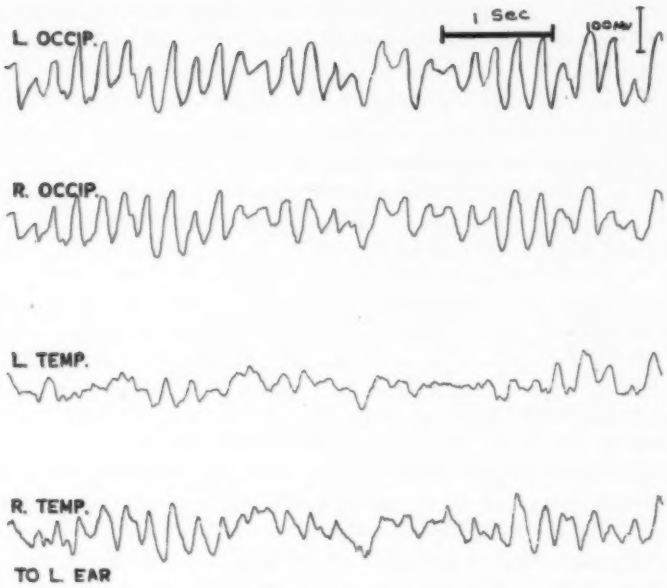

Fig. 1.—Abnormal EEG using scalp-to-ear leads on a 4-year-old white girl with hypertension at time of tracing.

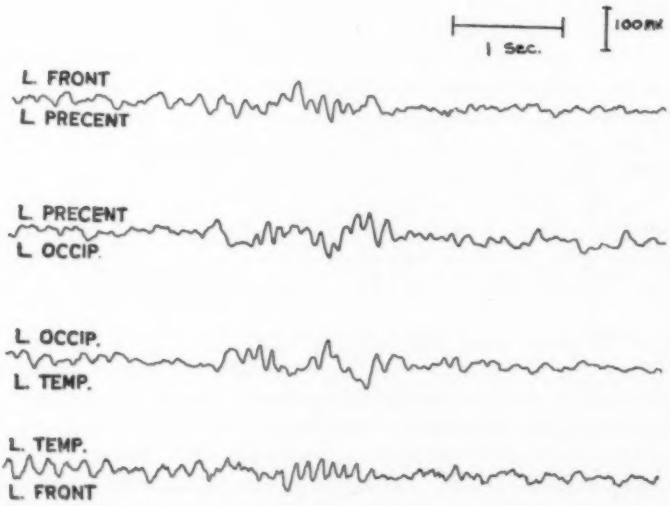

Fig. 2.—Abnormal EEG using scalp-to-scalp leads on an 11-year-old Negro girl with hypertension at time of tracing which shows instability and suppression of alpha.

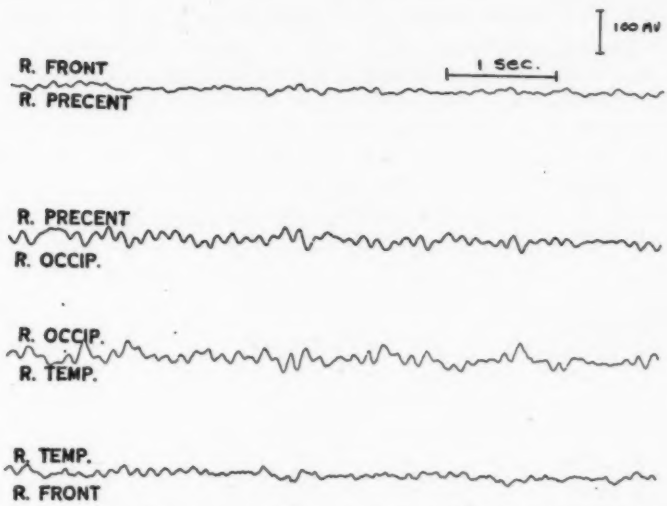

Fig. 3.—Normal EEG using scalp-to-scalp leads on a 12-year-old Negro boy with hypertension at time of tracing.

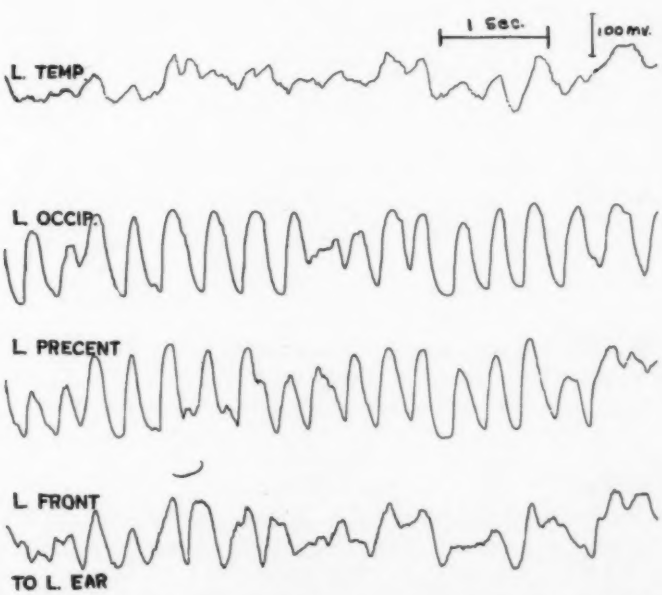

Fig. 4.—Abnormal EEG using scalp-to-ear leads on a 7-year-old Negro boy with normal blood pressure at time of tracing.

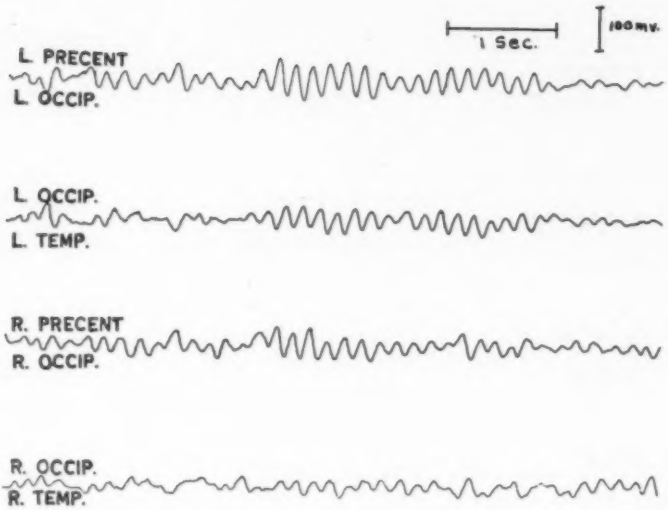

Fig. 5A.—Normal EEG using scalp-to-scalp leads on a 4-year-old Negro girl with hypertension at time of tracing.

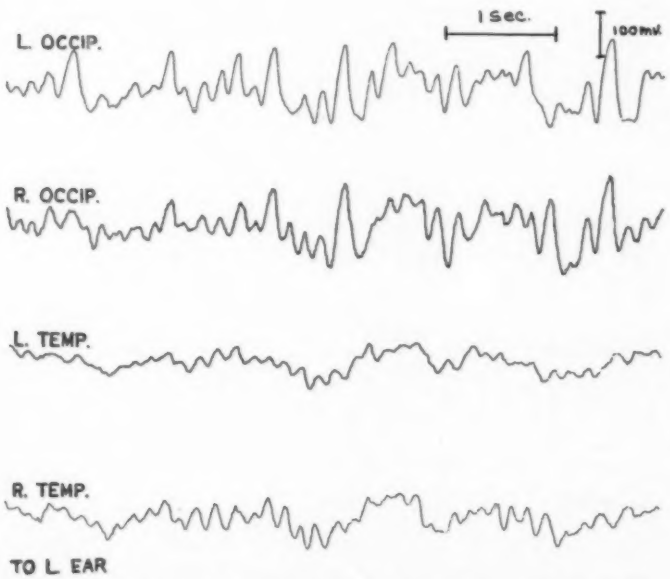

Fig. 5B.—Abnormal EEG using scalp-to-ear leads on the same patient as in 5A with hypertension at time of tracing.

Of the twenty-four children with acute nephritis, twelve had symptoms referable to the nervous system, consisting of headache and vomiting, and various changes in alertness ranging from stupor to drowsiness. Only two patients had convulsions, one immediately before admission and one on admission. Twelve of the children had no central nervous system symptoms. All of the twelve patients with nervous system symptoms had abnormal electroencephalograms, and ten of the twelve children without nervous system manifestations had an abnormal EEG. The degree of abnormality of the EEG in patients with nervous system symptoms was no greater than in those without such symptoms. This indicates that the electroencephalogram is a more sensitive indicator of cortical dysfunction in acute nephritis than is simple clinical observation.

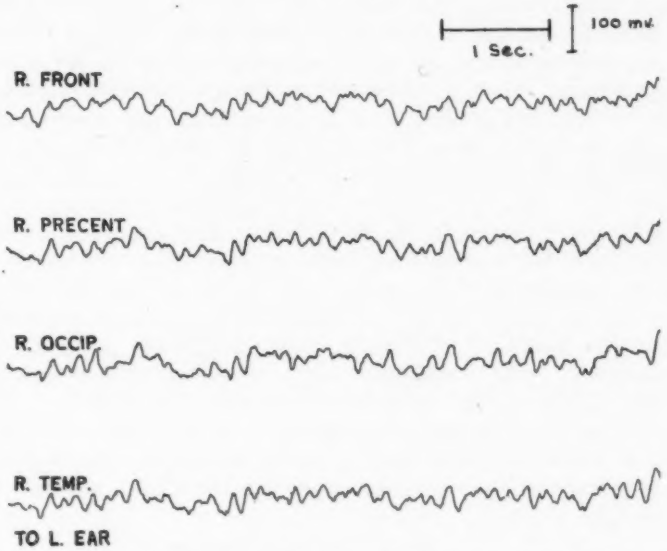

Fig. 5*C*.—EEG using scalp-to-ear leads taken on same patient as in 5*A* and 5*B* showing a return to normal with normal blood pressure at time of tracing.

Six of the twenty-four patients showed clear-cut cardiac failure accompanying acute nephritis. Abnormal electroencephalograms were encountered in all of these patients but to no greater degree than in other nephritic patients who did not have cardiac failure.

DISCUSSION

While these studies bear witness to the frequency with which the brain is involved in the pathologic physiology of acute nephritis, they do not clarify the cause of the cortical disturbance. That the alterations of brain potentials in patients with acute nephritis are probably due to tissue anoxia secondary to angiospasm seems likely. It is a familiar fact that central nervous system

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symptoms are generally associated in acute nephritis with marked elevation of the blood pressure, commonly considered to result from increase in peripheral resistance due to widespread arteriolar constriction. Furthermore, relief of hypertension by such an agent as magnesium sulfate, in amounts too small to have reduced presumed cerebral edema, brings about rapid improvement in central nervous system symptoms.

The work of Whitacre, Loeb, and Chin,[7] of Jost,[8] and of Jost, Ruilmann, Hill, and Gulo[5, 6] indicates that cortical anoxia is probably the basic cause of electroencephalographic abnormalities in patients with hypertension, especially in obstetric eclampsia.

We are of the opinion that in acute nephritis angiospasm of small cerebral vessels creates ischemia and anoxia of the cortex which give rise to the electroencephalographic abnormalities encountered. We have not yet had the opportunity to study children with acute nephritis in the manner most likely to clarify the question of whether cortical anoxia is the cause of the alterations in brain potentials. The type of patient with acute nephritis needing special study to cast light on this point is one having extreme hypertension and nervous system symptoms at the time of the first tracing. Serial electroencephalograms at frequent intervals over a period of hours during the phase of falling pressure would give more definite evidence as to whether relief of angiospasm probably accounts for improvement in the EEG. Observations on eye grounds during the reduction of hypertension are badly needed. Other techniques to study peripheral vasoconstriction during the lowering of the blood pressure would be helpful. Spinal fluid pressures correlated with venous pressures are needed to investigate the possibility of cerebral edema contributing to the alterations in brain potentials. These comments indicate the complexity of the investigations upon which clarification of the underlying abnormality depend.

Regardless of the pathologic physiology, it is clear that acute nephritis in children produces changes in brain potentials in the great majority of the patients. These changes may be observed if the patients are studied over a period of several days.

SUMMARY AND CONCLUSIONS

In twenty-four children with acute nephritis, 164 electroencephalograms were obtained. Electroencephalographic abnormalities were noted in twenty-two of the twenty-four patients.

The chief changes seen were bursts of slow frequency waves of high microvoltage, instability of the electroencephalographic pattern, and suppression of the alpha activity associated with an increase of fast frequencies of low amplitude.

The character of the electroencephalogram tended to vary from day to day, and this could not be correlated very well with the clinical condition of the patient. However, the data show that as acute nephritis persists day after day, there is increased likelihood of EEG abnormalities, with the brain potentials returning to normal as the nephritis recedes. Whether persistent EEG abnormalities may endure following acute nephritis has not been determined.

No direct correlation between degree of hypertension and electroencephalographic abnormalities was found, although the types of cases most likely to cast light on such a relationship were not studied.

The fact that twenty-two of our twenty-four children with acute nephritis showed abnormal brain potentials, whereas only twelve had nervous system symptoms, indicates that the technique of electroencephalography offers a more sensitive approach to the determination of the frequency of cortical dysfunction in this disease.

We are grateful for the technical assistance of Mrs. Glenn Morris Parry in recording many of the electroencephalograms.

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THYROID NEOPLASMS IN YOUTH

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BETWEEN 1922 and 1948, inclusive, twenty-three patients under 20 years of age with neoplasm of the thyroid were seen by members of the Thyroid Clinic of the University of California Hospital. In this series, there were four instances of benign tumor and nineteen of malignant tumor. The purpose of this report is to emphasize the clinical features of these cases and also the fact that malignancy of the thyroid, even in this age group, must be kept persistently in mind.

Hare[1] described six cases of carcinoma of the thyroid in patients under 14 years of age and pointed out that when metastases in the cervical nodes are the first abnormalities noted, although the differential diagnosis might include lymphoma and tuberculous adenitis, biopsy is essential. Kennedy,[2] in a series of sixty-two instances of nodular goiter in patients aged 14 years and younger, found twelve patients with carcinoma in seven of whom metastases were present, two patients with thyroiditis, and forty-eight with adenomatous goiter. The high occurrence of adenomatous goiters may be due to the fact that presumably his patients were from endemic areas. Rickles[3] encountered four cases of carcinoma of the thyroid in children during a four-year period in a small charity hospital in Florida.

Nontoxic nodular goiters which are neither neoplastic nor due to thyroiditis are termed involutionary. They occur as a result of a relative lack of iodine which may be due to residency in endemic areas or to the stress of puberty, pregnancy, or menopause. Additional changes, such as hyperplasia, hyperinvolution, or cyst formation (perhaps with hyaline, calcific, or hemorrhagic degeneration), may occur in the nodules. In our clinic, involutionary goiters have occurred in patients under the age of 20 years only nine times in a series of 771 patients with nontoxic nodular goiters. Therefore, if a nodular goiter is found in a youth, a neoplasm must be strongly suspected.

Table I presents the pertinent historical data and physical findings in our group of patients with benign nodular goiters. Table II presents the same data in our group of patients with malignant nodular goiters, plus the type of therapy employed and the survival periods. All the benign tumors and fifteen of the nineteen malignant tumors occurred in female patients; metastases were present in thirteen of the latter group. These nineteen malignant tumors represent 11.0 per cent of the total of 172 thyroid malignancies seen in this clinic in the past twenty-seven years. The benign tumors had been present an average of 21.2 months and the malignant tumors 31.7 months before definitive medical treatment.

Aided by a grant from the Donner Foundation, Cancer Division, Philadelphia, Pa.

From the Divisions of Medicine and Pathology, University of California Medical School, San Francisco.

TABLE I. BENIGN NEOPLASMS OF THE THYROID GLAND

CASE NO.	SEX	AGE (YR.)	DURATION OF GOITER	LOCAL SYMPTOMS	PHYSICAL FINDINGS	PATHOLOGIC DIAGNOSIS
1	F	17 19 12	3 years	Cough, hoarseness, slow growth	Multiple nodules	Multiple adenomas and involutionary nodules
2	F		2 years	Slow growth	Single nodule	Adenoma
3	F		1 month	Cough	Single nodule	Papillary adenoma
4	F	19	2 years	None	Single nodule	Intracystic papilloma

Goiters may cause a variety of pressure symptoms, including dysphagia, cough, dyspnea, choking, and hoarseness. The type of pressure symptom does not aid in the clinical diagnosis of thyroid tumors, except for hoarseness, which, if associated with vocal cord paralysis, is an ominous finding. Tracheal pressure and displacement by any type of goiter may cause hoarseness, but vocal cord paralysis, which is usually due to actual invasion of the recurrent laryngeal nerve, is found most frequently with malignancy. In another study[4] it was demonstrated that hoarseness occurs with nearly the same frequency in all types of goiter, but that in *patients with hoarseness* only 11 per cent of those with involutionary goiters had a paralyzed cord, while 75 per cent of those with malignancy did. Local tenderness and pain in the absence of thyroiditis are uncommon complaints unless hemorrhage has occurred in a cyst. However, several patients with carcinoma had no pressure complaints referable to the goiter.

In the age group considered here, the most important point at physical examination was the discovery of a nodular goiter. In Frantz's[5] series of nontoxic nodular goiters, 6.8 per cent were malignant; in our clinic 4.8 per cent were found to be malignant.[6] In our series, 12.5 per cent of all nontoxic nodular goiters in patients under the age of 20 years were benign, and 59.0 per cent were malignant. In adults, it was found that solitary nodules in the thyroid were malignant in 13.5 per cent of the cases. Any nodular goiter in youth, however, must be considered to be neoplastic, since the factors which cause the genesis of involutionary nodules have not been operative sufficiently long. This is all the more emphatically true in nonendemic areas.

We have followed, with minor modifications, the classification of thyroid tumors suggested by Warren.[7] Adenomas are of relatively homogeneous cellular structure, encapsulated, and differ distinctly in their gross appearance from the surrounding gland. They may be classified as embryonal, fetal, colloid, or papillary, depending on the dominant cellular pattern. An intracystic papilloma displays irregular papillary epithelial projections supported by delicate connective tissue stroma which extends from the cyst wall into the colloid-filled lumen. The cells of a malignant adenoma are anaplastic, mitotic activity and nuclear hyperchromatism are pronounced, and capsular invasion is present. Eleven malignant tumors in our series were clearly of a papillary pattern. However, a given tumor may not be entirely uniform in microscopic appearance.

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TABLE II. MALIGNANT NEOPLASMS OF THE THYR[OID] AND [M]

CASE NO.	SEX	AGE (YEARS)	DURATION OF GOITER	LOCAL SYMPTOMS	PHYSICAL FINDINGS	PATHOLOGIC DIAGNOSIS	MET
1	M	8	7 months	Dysphagia; growth	Diffuse enlargement	Papillary adenocarcinoma	rvical
2	F	8	7 months	Slow growth	Hard mass	Papillary adenocarcinoma with vascular invasion	rvical clavicul
3	F	9	2 months	Dysphagia, rapid growth	Single, hard nodule with soft enlargement of remaining gland	Papillary adenocarcinoma; Hashimoto thyroiditis	rvical
4	M	10	Operated upon 2 and 4 years previously in other hospitals for carcinoma	Slow growth since previous surgery	Matted nodes and hard thyroid mass	Alveolar carcinoma with vascular invasion	rvical
5	F	11	8 months	None	Single nodule	Papillary adenocarcinoma	rvical
6	M	12	2 years	Hoarseness	Single nodule	Papillary adenocarcinoma	rvical
7	F	14	11 years	Recent rapid growth of lateral nodules	Solitary thyroid nodule and cervical nodes	Papillary adenocarcinoma	rvical clavicul
8	F	15	2 months	Tender, rapid growth	Thyroid six times normal size	Papillary adenocarcinoma; Hashimoto thyroiditis	ne
9	F	15	3 years	Steady growth, hoarseness	Firm mass with tracheal deviation	Adenocarcinoma	ne
10	F	17	9 months	Cough	Single nodule	Adenocarcinoma with vascular invasion	ne
11	F	17	7 years	Hoarse; left Horner's syndrome	Large thyroid mass	Papillary adenocarcinoma	rvical
12	F	17	4 years	Slow growth	Single nodule	Carcinoma	rvical
13	F	17	8 months	None	Multiple nodules	Papillary adenocarcinoma	rvical
14	F	17	2 years	None	Single nodule	Malignant adenom	ne
15	M	18	3 years	Slow growth	Multiple hard nodules	Adenocarcinoma	rvical
16	F	19	2 years	Slow growth	Single nodule	Papillary adenocarcinoma with vascular invasion	rvical a clavicula
17	F	19	9 months	None	Single nodule	Papillary adenocarcinoma	rvical
18	F	19	5 years	Slow growth	Single nodule	Adenocarcinoma with vascular invasion	ne
19	F	19	3 years	Slow growth	Single nodule	Malignant adenom	ne

E THYR LAND WITH THERAPY AND SURVIVAL OF PATIENTS

LOGIC OSIS	METASTASES	THERAPY	SURVIVAL PERIOD FROM DIAGNOSIS	PRESENT STATUS
denocar-	rvical nodes, lungs	Total thyroidectomy; radiation; radioactive iodine	18 years	Multiple pulmonary metastases; pharyngeal mass
denocar- ith vas- asion	rvical and supraclavicular nodes	Total thyroidectomy; radical neck dissection 1 year later	2 years	No evident recurrence
denocar- Hashi- roiditis	rvical nodes	Total thyroidectomy and removal of involved cervical nodes	10 months	Normal at present (recently operated upon)
rcinoma ular in-	rvical nodes, lungs	Total thyroidectomy and removal of involved cervical nodes; radioactive iodine	2 years	Pulmonary metastases; no local recurrence
denocar-	rvical nodes	Total thyroidectomy; infrahyoid neck dissection; radiation	14 months	No evident recurrence
denocar-	rvical nodes	Total thyroidectomy. Reoperated upon 8 years later for recurrence along carotid sheath	8½ years	No evident recurrence after latest operation 6 months ago
denocar-	rvical and supraclavicular nodes	Total thyroidectomy and neck dissection	2 years	Alive (not recently examined)
denocar- Hashi- roiditis	ne	Thyroidectomy	20 years	No evident recurrence
oma	ne	Thyroidectomy	10 years	No evident recurrence
oma ular in-	ne	Partial thyroidectomy; radical thyroidectomy 2 years later for recurrence	4 years	No evident recurrence
denocar-	rvical nodes	Total thyroidectomy and removal of involved cervical nodes	3 years	No evident recurrence
	rvical nodes	Total thyroidectomy and removal of involved cervical nodes	6 years	No evident recurrence
denocar-	rvical nodes	Total thyroidectomy and removal of involved cervical nodes	2½ years	No evident recurrence
denoma	ne	Subtotal thyroidectomy	6 years	No evident recurrence
oma	rvical nodes	Thyroidectomy; radiation; radioactive iodine	3 years	Paraesophageal recurrence; myxedematous
denocar- ith vas- asion	rvical and supraclavicular nodes	Total thyroidectomy; radical neck dissection	2½ years	No evident recurrence
denocar-	rvical nodes	Total thyroidectomy and removal of involved cervical nodes	3 years	No evident recurrence
oma ular in-	ne	Subtotal thyroidectomy	7 years	No evident recurrence
denoma	ne	Subtotal thyroidectomy	14 years	No evident recurrence

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Among the young, adenocarcinomas and alveolar carcinomas are encountered, but we have not seen the highly anaplastic rapidly-growing carcinomas which are more characteristic of the aged. Of ten patients with tumors of this latter type, six were dead within an average of 14.2 months postoperatively. This is in distinct contrast to the survival periods of the age group under discussion. Areas of thyroiditis are not infrequently encountered in the malignant thyroid, and this association is represented by two cases in our present series (Fig. 1).

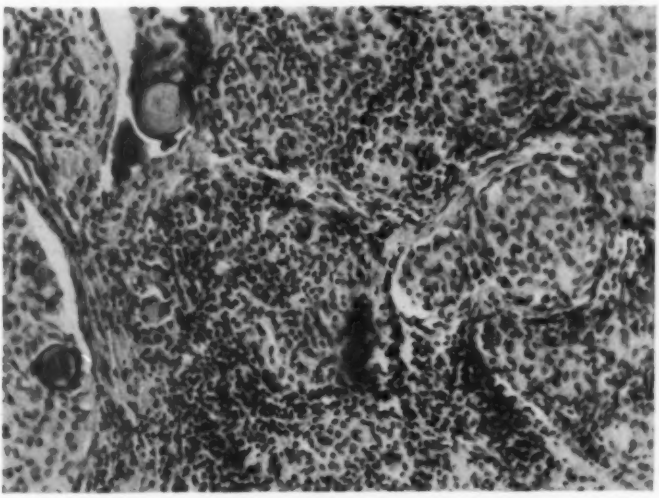

Fig. 1.—An example of carcinoma associated with diffuse chronic thyroiditis of the Hashimoto type. In the photograph are three infiltrating groups of neoplastic cells, two of which contain rounded calcific masses (Case 3). (×160, hematoxylin and eosin.)

Examples of the so-called lateral aberrant thyroid carcinoma are not seen in our patients. This type of malignancy in practically all cases is simply the initial manifestation of cervical metastases from a primary carcinoma in the thyroid gland. Thus, if the cervical metastases are the only recognized evidence of malignancy, a case might be considered to represent an instance of lateral aberrant thyroid carcinoma, while if, in addition, a firm thyroid nodule were palpable, the clinical diagnosis would be "carcinoma of the thyroid with cervical node metastases." We believe there is no distinction between such cases and, therefore, thyroidectomy is necessary whenever "lateral aberrant" thyroid carcinoma is diagnosed. Warren and Feldman[8] recently presented a fair and comprehensive survey of this problem and came to the same conclusion.

In general, subtotal thyroidectomy is indicated for all nodular goiters occurring in individuals under the age of 20 years because of the decided rarity of nonneoplastic nodules in persons under this age. The likelihood of malignancy is even greater if the nodule is solitary, if it has recently grown, or if it is associated with vocal cord paralysis. If malignancy is evident, radical thy-

roidectomy is carried out with removal of all involved lymph nodes and a radical neck dissection is frequently necessary. Reoperation is preferred for recurrences, especially of the papillary type of carcinoma, while radiation is reserved for inoperable tumors.

Long-term survival (see Table II) is possible even though local or visceral metastases are present. This fact is reason enough for an aggressive attack on this type of malignancy. Among adults, survival for several years after the discovery of remote metastases is not at all unusual.

Radioactive iodine has been used experimentally in the therapy of three patients reported here. Since this agent has been available, test doses of radioactive iodine (I^{131}) have been given to all patients suspected of having carcinoma of the thyroid. In less than 10 per cent of all cases, a sufficient uptake has occurred in the tumor, as proved by the surgical specimens, to warrant therapeutic trial. Our attempts to increase uptake in metastases by total thyroidectomy, low-iodine diet, or the administration of thyrotropic hormone have not been successful. Therapy with radioactive iodine may be beneficial at times, but is distinctly an adjunct to adequate surgery.

CONCLUSIONS

1. All nodular goiters in children and youths should be extirpated because of the grave possibility of neoplasm.

2. Gratifying survival may occur even in the presence of local or distant metastases.

3. In rare instances, radioactive iodine may be used as an adjunct to surgery, but the scope of its value is not yet established.

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THE ELECTROCARDIOGRAMS OF ONE HUNDRED NORMAL INFANTS AND YOUNG CHILDREN

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MANY investigations have been made of the electrocardiograms of young children, but few large series of those of children under the age of 4 years have been reported. This has resulted in a lack of adequate standards for the reading of electrocardiograms of infants and young children, especially with reference to the precordial leads. It is the purpose of this paper to add to the present data accurate measurements of all components of one hundred cardiograms of children between the ages of 12 hours and 4 years. Emphasis is laid on the group of children in the neonatal age range for two reasons: first, because this group seems to have been studied least; and second, because it is here that standards are needed most, since at this age the cardiograms exhibit the greatest variations from the adult normal tracings. In addition, with the rapid advances now being made in cardiac surgery, it has become increasingly important to have accurate standards with which to compare the electrocardiograms of infants with congenital lesions. The correct diagnosis of congenital cardiac anomalies is no longer of purely academic interest, and the type of defect must be determined early in order to plan a course to be followed until the optimum time for surgery arrives.

The earliest significant work on children's electrocardiograms was done in 1908 by Nicolai and Funaro, who recorded the presence of a deep S wave in Lead I, and by Heubner who confirmed this observation, and noted a concomitant low R wave in Lead I. In 1913 Hecht observed that the time necessary for the transmission of the cardiac impulse throughout the heart is shorter in children than in adults, and that this is a greater difference than can be accounted for merely by the more rapid heart rate of the child. In 1916, Krumbhaar and Jenks called attention to the deep Q waves often found in the child's electrocardiogram. In the twenty years from 1920 to 1940, a number of interesting studies were done on school children. One of the best of these was that done in 1936 by Hafkesbring, Drawe, and Ashman,[6] and in this article can be found references to similar research by other investigators. The same year, one of the earliest studies of the precordial leads in children was made by Master, Dack, and Jaffe,[8] and since this time a number of other studies have been made. Comparison of the results of these and other recent studies with our results will be made hereafter.

METHODS

For this study, 100 normal infants and young children were taken at random from the newborn nursery, the well-baby clinic, and the pediatric clinic of the Children's Hospital for Women and Children, San Francisco. The children

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came, for the most part, from families of lower middle class income groups, since our clinic is on a part-pay basis. They were therefore in a nutritional state comparable with the average American children of their ages. There were forty-five girls and fifty-five boys in the series, of whom thirteen were Negroes, and three Orientals. The largest group of children was that in the newborn age range from 12 hours to 7 days; there were forty-eight of these. The group from 8 days to 4 months included twenty-four babies. There were nineteen older infants between the ages of 5 months and 12 months. Nine children between the ages of one and 4 years were studied.

A careful history was obtained from the parent in each case, and children who had had any cardiac symptoms or history of heart disease were excluded from the study. Children with major congenital defects other than cardiac were also excluded. The cases obtained from the pediatric clinic were children who came in for routine physical examinations or those who had minor complaints.

In order more definitely to exclude cardiac pathology, each child had either an x-ray of the chest or fluoroscopy of the chest with a barium swallow. Sixty-eight of the children had chest fluoroscopy, and thirty-two had chest x-rays. None of the children selected had to be excluded from the study on the basis of the chest x-ray, although a number of large thymus glands were found. The cardiothoracic ratio was measured in each case, and the lung fields were surveyed.

Electrocardiograms were obtained with the children in the recumbent position. The following leads were used: I, II, III, aV_R, aV_L, aV_F, aV_{R3} (a precordial lead just to the right of the sternum in the third interspace), V_1, V_2, V_3, V_4, V_5, V_6, V_7, and V_8. Children's small-sized electrodes were used, and care was taken to wipe the chest free of electrode paste between each application of the electrode. A direct-writing Sanborn electrocardiograph was used. The standardization of the machine was checked and adjusted, if necessary, before each lead was recorded.

Measurements were made of the following values in each electrocardiogram: rate and rhythm, position of the heart, electrical axis of the heart, amplitudes of all the waves, duration of all intervals, including the intrinsic deflection, and ratio of the amplitude of the R wave to that of the S wave. The measurements were all made with the aid of a hand magnifying glass and were checked for accuracy either by the person who made the first measurements or by another investigator.

In the summary of the results which follows, measurements of the amplitudes of the complexes are in millimeters, and those of the time intervals are in seconds. In the cases of waves such as the P and T, which may be either upright or inverted, it is assumed that all are upright unless preceded by a minus sign.

For purposes of comparison, the cases have been separated by age into four groups:

Group I: 0 to 7 days old.
Group II: 8 days to 4 months old.
Group III: 5 months to 11 months old.
Group IV: 1 year to 4 years old.

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TABLE I. MEAN AMPLITUDE OF P WAVES

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}	V_1	V_2	V_3	V_4	V_5	V_6	V_8
Group I	0.68	1.25	0.50	0.18	0.80	−0.86	0.66	0.68	0.76	0.82	0.83	0.77	0.58	0.29
Group II	0.78	1.10	0.34	0.28	0.80	−0.70	0.62	0.43	0.57	0.89	0.71	0.56	0.48	0.31
Group III	0.87	1.13	0.57	0.32	0.87	−0.82	0.47	0.70	0.92	0.85	0.72	0.63	0.65	0.46
Group IV	0.76	1.10	0.52	0.37	0.93	−1.10	0.72	0.72	0.51	1.1	0.90	0.61	0.58	0.40
Adults	0.55	1.25	0.80*	(Ashman and Hull)										
Children	0.70	1.31	0.588	(Hafkesbring, Drawe, and Ashman)										

RESULTS

P Waves.—As can be seen by inspection of Table I, the mean amplitude of the P waves in the standard leads in these young children is significantly higher than the adult mean amplitude, but not much different from the mean amplitude for older children, as given by Hafkesbring, Drawe, and Ashman.[6]

Lincoln and Nicolson,[7] however, noted much higher P-wave amplitudes in the standard leads in children between the ages of 3 and 7 years. Seham and Moss[9] draw attention to an abrupt increase in amplitude of the P wave in Lead III to about 1 mm. in the first few months after birth. Our figures do not corroborate this observation, P_{III} remaining below 0.6 mm. throughout the first year. The mean amplitude of the P waves in the precordial leads of our series was greatest in the region of the transitional zone, in contradistinction to the situation prevailing among the 2- to 17-year-old children studied by Master, Dack, and Jaffe,[8] who found the largest P waves in Leads V_1 and V_2.

Inspection of Table II will indicate the presence of Inverted P waves in Lead III. It will also indicate that in the older children of our series, the expected inversion of the P wave in Lead V_1 was not found. In addition, it can be seen that the range of P-wave amplitudes is greater in the children than in adults, with the largest amplitudes in our series occurring in the newborn group. The increased P waves in the newborn children are understandable when one considers the large size of the auricles in relation to the size of the ventricles at birth.

Q Waves.—Although the Q wave was absent from Lead I in the majority of electrocardiograms, our findings do not agree with those of Seham and Moss[9] who, in a series of 101 normal children, noted that Q was totally absent during the first month of life, and never larger than 0.7 mm. during the first five months.

The accompanying tables will show that in our series, 20 per cent of the newborn infants had Q waves in Lead I ranging from 0.2 mm. to 6.4 mm. deep, and 33.3 per cent of the children between the ages of 8 days and 4 months had Q waves which ranged in amplitude from 0.2 to 2.0 mm.

Q waves, when present in the standard leads, were found to be larger than is considered normal for adults. However, in such cases the large R waves characteristic of children's cardiograms were present, and Q was never greater than 25 per cent of the height of the R wave. These findings agree with those of Ash,[1] who noted similar large Q waves in her study of the precordial leads of 150 children. Fig. 1 illustrates this type of pattern of large Q and R waves in Lead II of a 4-month-old boy. In series of older children, such as that of Lincoln and Nicolson,[7] which included 222 children between the ages of 3 and 12 years, a gradual decrease of amplitude of Q waves with increase in age is noted until the adult values are reached after the age of 8 years.

Although the augmented unipolar extremity leads reflect the increased amplitude of the standard leads, the left arm lead consistently shows more absent Q waves than standard Lead I. It is beyond the scope of this paper to go into the electrical principles causing this. Those interested are referred to the many excellent discussions of the unipolar limb leads by Goldberger.[3]

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TABLE II. RANGE A

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}
Group I	0.2 to 2 0.5	0.3 to 2.5 1.2	−1 to 1.5 0.5	−0.5 to 1.3 0.2	−0.2 to 1.5 0.8	−2 to −0.3 −1	−0.6 to 1. 0.
Group II	0.2 to 1.7 0.7	0.1 to 1.8 1	−0.3 to 0.6 0.4	−0.2 to 0.8 0.2	0.2 to 1.5 0.8	−1.9 to 1.2 −0.9	−0.2 to 1 0.
Group III	0.5 to 1.5 1	0.5 to 1.8 1	0.3 to 1.3 0.5	−0.3 to 0.6 0.4	0.2 to 2 1	−1.1 to 0.4 −0.8	−1 to 2 0.5
Group IV	0.3 to 1 0.8	0.5 to 1.8 1.2	−0.5 to 1 .5	−0.2 to 1 0.35	0.2 to 1.5 1	−2 to 0.3 −1.2	0.5 to 1 0.

TABLE III. ME

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}
Group I	80% ab	1.20	1.8	94% ab	1.42	62% ab	98% ab
Group II	67% ab	1.22	1.8	87% ab	1.33	71% ab	100% ab
Group III	83% ab	.95	2.8	89% ab	1.50	54% ab	100% ab
Group IV	100% ab	1.2	2.3	100% ab	1.5	40% ab	89% ab
Adults	0.36	0.58	0.61				

TABLE IV. RANGE A

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}
Group I	0.2 to 6.4 80% ab	0.2 to 4 1.0	0.4 to 7.7 1.5	1.5 to 4.2 94% ab	0.3 to 3.8 1.25	0.6 to 4.5 65% ab	0.1 to 0. 98% ab
Group II	0.2 to 2 66% ab	0.3 to 2.6 1	0.3 to 4 1.8	0.5 to 1 87% ab	0.2 to 2.7 1.45	1.3 to 9.5 71% ab	100% ab
Group III	0.5 to 1.3 83% ab	0.1 to 3 0.5	0.4 to 7.5 1.5	1 89% ab	0.2 to 4.9 1	5.5 to 9 54%	100% ab
Group IV	100% ab	0.2 to 3 1	1.2 to 3.5 2.3	100%	0.2 to 4.5 1.2	8 to 12.6 40% ab	0. 89% ab
Adults	0 to 2	0 to 2.5	0 to 3				

Progressing to the precordial leads, we find that Q can be considered for all practical purposes to be completely absent in the first three precordial leads, and frequently to be absent when the electrode is over the cardiac apex. Miller and Groedel[5] noted absence of the Q wave with the electrode at the left axillary line in 66 per cent of their cardiograms taken immediately after birth, with appearance of a Q wave twelve to twenty-four hours later in half of these cases, the other half continuing to show no Q wave for several weeks after birth. Our group showed an absent Q in V_6 in 81 per cent of infants from 12 hours to 7 days of age. Again in the precordial leads we find Q waves that are larger than the largest ones in normal adults, but inspection of the individual records shows that these occur only in cases of very large R waves.

Electrical Axis and Cardiac Position.—Before consideration is given to the remaining components of the ventricular complex, it seems advisable to review the findings in relation to the electrical axis and cardiac position in these young children. Our findings in regard to the electrical axes of the hearts are in accordance with those of other workers, i.e., the electrical axis of the heart shows predominantly right deviation after birth, and during infancy the axis changes gradually to a normal one.

DIAN P WAVE AMPLITUDES

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
2 to 2 0.7	−1 to 2.3 0.8	−0.6 to 2.5 0.75	−0.3 to 2.3 0.8	0.2 to 1.8 0.8	0.1 to 1.4 0.5	−0.2 to 1 0.35	−0.1 to 0.7 0.2
3 to 1 0.6	−0.2 to 1.5 0.5	0.2 to 2 0.8	0.2 to 1.2 0.75	0.1 to 1 0.5	0.1 to 1 0.5	0.1 to 2 0.3	0.1 to 0.9 0.25
5 to 2 0.8	0.3 to 3 0.7	0.3 to 1.7 0.5	0.3 to 1.3 0.5	0.3 to 1.5 0.5	0.2 to 2 0.5	0.2 to 2 0.5	0.2 to 1 0.5
2 to 1.5 0.5	0.4 to 0.7 0.5	0.3 to 2 1.06	0.5 to 1 1	0.4 to 1 0.5	0.2 to 1 0.5	0.3 to 0.5 0.5	0.1 to 1 0.3

PLITUDES OF Q WAVES*

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
100% ab	100% ab	100% ab	98% ab	89% ab	81% ab	80% ab	77% ab
100% ab	100% ab	100% ab	83% ab	42% ab	35% ab	30% ab	1.55
95% ab	93% ab	100% ab	40% ab	33% ab	1.3	1.2	1.82
100% ab	100% ab	100% ab	86% ab	1.5	1.3	1.1	1.24
100% ab	100% ab	0.04	3	3.4			

*ab = absent Q wave.

DIAN Q-WAVE AMPLITUDES*

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
100% ab	100% ab	100% ab	0.6 98% ab	0.2 to 1 89% ab	0.2 to 1 81% ab	0.1 to 1 80% ab	0.1 to 6.4 77% ab
100% ab	100% ab	100% ab	0.5 to 1.3 83% ab	0.1 to 2.3 42% ab	0.2 to 2.2 35% ab	0.1 to 2.2 30% ab	0.2 to 4.2 1.4
2 95% ab	2 93% ab	100% ab	0.5 to 5 40% ab	0.2 to 3.3 33% ab	0.3 to 2.7 1.3	0.5 to 2 1	0.4 to 3 2
100% ab	100% ab	100% ab	0.5 to 0.6 86% ab	0.5 to 3 1.1	0.5 to 2.5 1.5	0.8 to 1.5 1	0.7 to 1.8 1.5

*ab = absent Q wave.

As would be expected, vertical and semivertical positions predominate. The finding of an occasional horizontal position in the group of newborn infants seems best explained by the combination of less rotation of the heart than usual together with the high diaphragm of the newborn infant.

A good deal of variation exists in the electrical axes and cardiac positions of the children, probably due to differences in the relative rates of growth of the two ventricles in different individuals.

R Waves.—The R waves of children, as is well known, tend to be much larger than those of adults, and those in our series were of expected amplitudes. The tallest R in the series was found in Lead V_4 in a 7-month-old male infant, and was 34.1 mm. in height. The R waves were slightly higher in the group between 5 and 11 months of age than in either of the adjacent age groups.

In Leads I, II, aV_L, and the left precordial leads, the R waves of the newborn infants were definitely lower than those of the other groups (see Table VII), and their R waves in the leads to the right of the sternum were significantly higher than those of the other children. These differences can probably be explained by the large muscle mass of the right ventricle in relation to the

TABLE V. CARDIAC AXIS

	GROUP I	GROUP II	GROUP III	GROUP IV
Right axis (% of total)	87.5	33.3	0	12.5
Normal axis (% of total)	8.25	66.7	100	87.5
Left axis (% of total)	4.25	0	0	0
Mean axis	+108	+81	+61	+75
Median axis	+115	+84	+67.5	+73
Range	+175 to −125	+130 to +26	+88 to +22	+94 to +64

TABLE VI. POSITION OF THE HEART

GROUP I	GROUP II	GROUP III	GROUP IV
41 vertical	19 vertical	7 vertical	2 vertical
2 semivertical	4 semivertical	9 semivertical	7 semivertical
2 semihorizontal	1 intermediate	2 intermediate	
1 horizontal		1 semihorizontal	
2 indeterminate			

left ventricle in the newborn infant, as compared with its insignificance in relation to the thickness of the left ventricle in the adult. In the newborn infant the weight of the right ventricle is one-third that of the left, while in the adult it is one-thirteenth as heavy as the left ventricle.

In accordance with the right axis deviations and vertical hearts commonly found in our series, the R waves in the right precordial leads were, in many cases, taller than the S waves in the same leads, and also taller than the R waves in the left precordial leads. Fig. 2 shows a cardiogram of this type in a 4-day-old boy.

In a number of the electrocardiograms of our normal children, M-shaped QRS complexes were noted in leads V_{R_3} and V_1 (see Fig. 3). In most instances the noteh of the M was not deep enough to return to the isoelectric line before the second upward deflection began. The same phenomenon was also noted by Ash[1] in her series, and was considered by her to be due to the magnitude of variations in potential in the left leg when this is used as the remote electrode.

TABLE VII. MEA

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}
Group I	1.49	5.2	8.4	1.9	6.67	2.94	10.19
Group II	5.18	9.75	7.7	2.8	8.12	2.18	7.91
Group III	7.82	11.4	6.6	3.78	8.44	2.44	5.98
Group IV	6.22	13.56	9	2.61	11.58	1.74	4.44
Adults	5.5	11.5	7				

TABLE VIII. RANGE AN

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}
Group I	0.1 to 11 0.9	0.4 to 12.8 5.3	2.8 to 16 7.9	0.2 to 15.8 1.3	1.8 to 16.7 6.7	0.3 to 9.2 2.9	3 to 22 9.
Group II	0.5 to 11 5.4	2.8 to 17.3 10	2 to 15 8.2	0.5 to 5.5 2.95	4 to 15.4 7.7	0.3 to 7 1.5	1.5 to 17. 7.
Group III	1.2 to 12 8	5.9 to 22.3 10	1.2 to 17 5.5	1 to 10 3	2.7 to 21.7 7.5	1 to 4.3 2.2	2.4 to 11 5.
Group IV	3 to 9.5 6	9.5 to 18.4 13	5 to 14 9	1.2 to 4.8 2.5	8 to 16 10.3	0.8 to 3.9 1.5	0.4 to 11. 4.
Adults	1.5 to 12	4 to 23	1 to 20				

Goldberger[3] emphasizes that the pattern may be considered normal when the final R′ of Lead V_1 is thin, and less than 0.04 second wide at the base. In all of our cases these criteria were fulfilled.

In the series of older children studied by Master, Dack, and Jaffe,[8] notching and slurring of the QRS complexes were observed in the precordial leads. In our series, some children in all of the age groups were found to have notching or slurring in some of their QRS complexes, usually in Lead V_{R_2} or V_1. However, in no normal child was notching or slurring found in all or in a majority of the precordial leads, and in most it occurred in only one.

S Waves.—S waves in children are, on the whole, larger than those in adults; and the largest are found in the youngest children.

In the standard leads (see Table IX), a deep S in Lead I was found in the newborn infants, as would be expected in view of the many right axis deviations in this group. In most of the cardiograms, S was absent in Lead III, and in all cases except one which showed left axis deviation, it was relatively small. In older children, the S waves in the standard leads gradually decrease in amplitude until the normal adult values are reached.

In the precordial leads, the S waves increase in depth as the electrode is moved across the chest until the third or fourth position is reached; then they decrease until they are absent in Lead V_6 in most of the children over the age of one week. The vertical position of the hearts is reflected by the small size of S as compared with the size of R in the right precordial leads (compare Tables VII and IX), and the opposite in the left precordial leads. Also, since the muscle mass of the right ventricle is great in relation to that of the left ventricle immediately after birth, one would expect the R wave to be larger than the S.

Table XI will enable comparison of the relative amplitudes of the R and S waves at the different ages studied.

MPLITUDES OF THE R WAVES

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
10.3	10.4	10	9.5	7.2	4.5	2.8	1.77
8.65	13.5	16.2	19	14.1	9.7	6	3.23
8.12	16.7	17.5	21	14.6	11	6.9	3.28
6.48	11.25	16.6	21	21.9	15	10.4	5.55
0.96	2.98	5.5	5	3.3			

EDIAN R-WAVES AMPLITUDES

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
9 to 21.6	3.8 to 24.8	1.7 to 25	2.4 to 19.4	1.8 to 15	0.2 to 11.1	0.3 to 10	0.1 to 11.5
9.2	10	9.5	8.5	6.7	3.85	2.2	1.2
5 to 19	6.9 to 26.2	7.7 to 27	4.8 to 29.4	2.8 to 27	2.9 to 17.7	0.3 to 14.5	0.2 to 11.9
7.5	13.8	15.8	19	14	10	4.4	2.5
to 18	6.2 to 25.4	10 to 24	8.5 to 34.1	7.7 to 30	4.5 to 25.5	1.5 to 16	0.2 to 9.2
7	17	18	19.8	14	11.4	6.8	2.9
to 11.5	7.4 to 21	7 to 25	8.6 to 27.2	16 to 28	10.6 to 18.8	8 to 13	2 to 9
6.48	6	17	22	22	16	10	4.5

TABLE IX. ME

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{E1}
Group I	4.89	5.9	68% ab	6.39	59% ab	53% ab	6.52
Group II	3.35	1.8	71% ab	4.53	50% ab	8.4	4.4
Group III	2.96	2	63% ab	3.54	1.14	54% ab	3.64
Group IV	2.35	1.7	55% ab	3.45	1.03	60% ab	4.75
Adults	1.5	1.7	1.5				

TABLE X. RANGE AN

LEAD	1	2	3	V_L	AV_F	AV_R	V_{E1}
Group I	1.8 to 11 4.7	0.2 to 10 2.3	0.2 to 19.2 68% ab	2.3 to 15.5 5.9	0.4 to 15.8 59% ab	0.3 to 7.9 53% ab	0.3 to 20 5
Group II	0.5 to 8.6 3.3	0.3 to 5.9 1.2	0.2 to 1.8 71% ab	1 to 8 4.4	0.2 to 3 50% ab	1.8 to 13.1 7.4	0.2 to 11 4
Group III	0.3 to 8 3	0.7 to 4 1.8	.25 to 3 63% ab	1 to 8.9 3.4	0.3 to 3 1	8.1 to 13.9 54% ab	0.1 to 9 3
Group IV	1 to 4.6 2	0.3 to 4.2 1.5	0.5 to 1 55% ab	1 to 8.5 2.5	0.2 to 2.2 0.9	7.3 to 10 60% ab	1.5 to 10 4
Adults	0 to 6	0 to 6	0 to 6.5				

TABLE XI. ME

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{E1}
Group I	0.25	3.5	16.5	0.22	3.74	1.81	5.27
Group II	2.2	11	15.7	1.7	18.8	0.25	5.18
Group III	3.4	7.4	8.59	1.6	13.6	0.24	5.23
Group IV	3.3	13	11.3	1.1	19.1	0.12	0.88

TABLE XII. ME

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{E1}
Group I	0.96	1.43	0.56	0.46	1.34	−1.32	−2.2
Group II	2.5	2.52	0.73	0.86	1.45	−2.13	−2.4
Group III	1.9	3.35	1.2	0.98	2.15	−2.37	−2.5
Group IV	2.36	3.1	0.78	0.93	1.84	−0.97	−2.4
Adults	2	3	1.2				

TABLE XIII. RANGE AN

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{E1}
Group I	−0.7 to 2.2 1	−1.5 to 3.5 1.4	−1 to 3.2 .45	−2 to 2.2 0.6	−1.7 to 2.9 0.85	−3.2 to 1 −1.2	−6 to 4.5 −3
Group II	0.8 to 3.3 2	1.5 to 5 2.5	−0.5 to 2.2 0.75	−0.6 to 2.5 0.8	0.2 to 3.8 1.4	−3.5 to −1 −2	−6.5 to 1 −2.5
Group III	1 to 4 2.4	1.3 to 6.5 3.2	−0.6 to 3.5 1.2	−1.5 to 2 1	0.7 to 4 1.95	−4.6 to 2.5 −3	−4.6 to 1.5 −2.5
Group IV	0.6 to 5 2.5	1.5 to 5.5 2.7	−1 to 1.7 1	−0.5 to 1.6 1	0.6 to 3.7 2	−5 to 2.8 −3	−5 to 0.5 −2.5
Adults	−0.5 to 5.5	0 to 8	−2 to 5.5				

PLITUDES OF S WAVES*

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
7.59	10.6	10.8	12.2	9.9	6.56	5.3	4.51
5	11.2	13.7	12.8	7.2	4.34	2.3	67% ab
6.14	11.4	12.8	8.5	4.7	2.1	1.4	76% ab
6.95	15.1	13.8	12.3	3.9	1.7	0.9	88% ab
2.4 max	3.8 max	2.2 max	1.6 max	0.96 max			

*ab = absent; max = maximum normal amplitude.

DIAN AMPLITUDES OF S WAVES*

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
to 20.4 6.3	0.6 to 26.6 10	1.2 to 31 11	1.2 to 26.2 11.5	0.3 to 20.9 9.1	0.6 to 18.3 6	0.2 to 15.5 5	0.2 to 14 3
to 12.6 4	3.3 to 20.8 11.5	4.6 to 22 15	5 to 21.6 12.2	2.6 to 19.6 6.4	0.5 to 13.7 3.6	0.5 to 8.5 2	0.5 to 5.9 67% ab
to 14 5.45	4 to 22 10	4 to 29 12	2.3 to 18 8.2	0.5 to 14 4.1	0.4 to 5.5 1.5	0.2 to 3.5 1.2	.02 to 4 76% ab
to 9.5 6.5	9.5 to 22 15	5.5 to 21 11.9	7 to 20.5 10	2.5 to 5.6 4	0.2 to 3.5 1.7	0.5 to 1.5 1	0.9 to 1 88% ab

*ab = absent.

S RATIOS

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
4.05	1.56	1.4	1.13	1.2	1	0.96	0.41
2.49	1.37	1.4	1.72	2.5	3.84	4.35	2.69
1.89	1.67	1.5	3.15	5.5	9	10.9	4
0.95	1.44	1.8	5.94	17	17	14.6	8

PLITUDE OF T WAVES

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
-2	-1.93	-1.2	-0.4	0.6	0.78	0.67	0.55
-2	-2.29	-1	2.4	2.6	2.2	1.53	0.81
-3	-2.1	0.53	2.2	3.2	2.6	1.86	1.03
-3	-2.72	-0.5	2.8	4.1	3.2	2.65	1.35

DIAN T-WAVE AMPLITUDES

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
8 to 4.5 -3	-5.5 to 3.4 -2.7	-4 to 4.2 -2	-4.5 to 3.3 -1.9	-2 to 2.2 -0.8	-0.8 to 2.2 0.75	-0.6 to 1.8 0.9	-0.4 to 1.2 0.5
to -1 -2.5	-4.6 to 2.9 -2.2	-4 to 3.6 -1	-1.5 to 4.8 2.5	-0.3 to 5.2 2.2	0.4 to 4.8 1.7	0.3 to 3.4 1.5	0.2 to 2 0.7
to 3.4 -3	-4.2 to 4 -2.5	-5 to 6 0.9	-6 to 6.2 2.6	0.5 to 6 2.8	1.2 to 4.7 2.5	0.7 to 3.8 1.8	-1 to 1.5 1.1
to 0.5 -3	-4.8 to -1.3 -2	-4 to 3.5 -0.4	-1.5 to 7.3 2.5	1.3 to 8 3.8	1 to 7 3	0.8 to 5 3	0.4 to 3.1 1.2

T Waves.—Negative T waves in standard Leads I and II, which generally are considered abnormal, were found in one case each in the group of newborn infants; and in Lead I in one case and Lead II in two cases the T wave was diphasic in this same group. T in Lead III was frequently inverted or diphasic in all groups. The amplitudes of the T waves in all leads were quite variable, and in general were greater than those for adults. No notched or slurred T waves were found.

Suarez and Suarez[10] made a study of T waves in the precordial leads of older children between the ages of 5 and 11 years. They concluded from this that a negative deflection is found normally in many children in V_1, but that by the time the electrode has reached the V_6 position, all T waves written should be upright. However, Battro and Mendy,[2] in their series of younger children up to the age of 2 years, found inverted T waves in 20 per cent of the cases as far to the left as V_6. Table XIII will show that in our youngest group of children negative T waves were found all the way across the precordium, those in the left precordial leads being low.

Goldberger[4] draws attention to the fact that it is in the precordial leads which face the epicardial surface of the right ventricle that one gets a ventricular complex consisting of R and S waves followed by an inverted T wave. Fig. 4 illustrates this type of ventricular complex; it is from the cardiogram of a 2-year-old female child. Because of the cardiac position and the relative preponderance of the right heart in young children, such patterns are found farther to the left in them than in older children and adults. In none of our records which showed inverted T waves did we find the QR or QRS pattern produced by precordial leads facing the epicardial surface of the left ventricle. Such an association would be considered abnormal by Goldberger. It can be seen from our records that the negativity of the inverted precordial leads decreases as one moves the electrode across the chest to the left.

Cardiac Rate and Rhythm.—Preliminary to discussion of the various time intervals of the electrocardiograms, some consideration should be given to the heart rates of the group of children studied, since the time intervals are in large part dependent upon these. And in conjunction with the rates of the hearts, their rhythms should be noted.

The rapid heart rate of the baby is well known. Infants in the age group from 3 weeks to 4 months had the highest rates, ranging from 125 to 209 beats per minute and averaging 163 beats per minute. The rate for the oldest children may be artificially slightly elevated, since these children were old enough to respond emotionally to the unusual circumstances of the test.

The incidence of sinus arrhythmia increased in our group with increasing age, and would probably have become even more frequent had we extended our age range to the years of middle childhood.

P-R Interval.—There was not much variation in the P-R intervals of different leads within the same age group. The expected lengthening of the P-R interval with increasing age and decreasing heart rate can be seen by compari-

son of the four age groups of Table XVI. Miller and Groedel[5] found that the average duration of the P-R interval increased during the first four months of life to 0.12 second. Our subjects, however, had not reached an average of so great a duration by the end of the first year.

QRS Interval.—Like the other time intervals, the QRS duration increases with age and with decreasing heart rate. Again, our durations are slightly shorter than those of Miller and Groedel,[5] who found that by the age of 4 months,

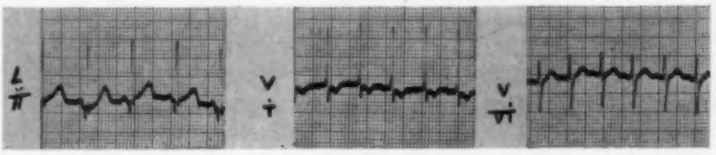

Fig 1. Fig. 2.

Fig. 1.—Pattern of large Q and R waves in Lead II of a 4-month-old boy.

Fig. 2.—An electrocardiogram showing a series in which R waves in the right precordial lead were taller than the S waves in the same lead, and also taller than the R waves in the left precordial lead. Subject was a 4-day-old boy.

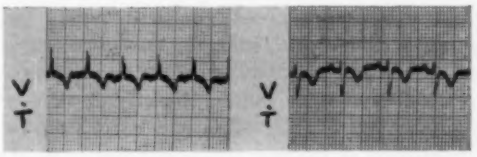

Fig. 3. Fig. 4.

Fig. 3.—Electrocardiogram showing M-shaped QRS complex in leads V_{R3} and V_1.

Fig. 4.—Electrocardiogram of a 2-year-old girl illustrating ventricular complex; it is in the precordial leads which face the epicardial surface of the right ventricle that one gets a ventricular complex consisting of R and S waves followed by an inverted T wave.

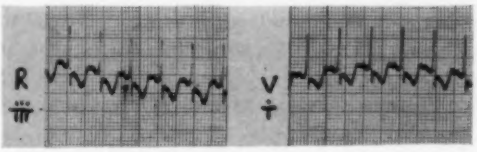

Fig. 5.

Fig. 5.—Electrocardiogram in which there is no apparent S-T interval; in such cases the termination of the R or S wave slopes directly upward or downward to form the anterior limb of the T wave.

the average duration of the QRS interval was 0.06 second. In our series children under the age of one year did not have QRS intervals lasting as long as 0.06 second.

Intrinsic Deflection.—The duration of the intrinsic deflection for most of the leads at all ages was in the neighborhood of 0.02 second. However, owing to the presence of slurring and double upward deflections in the right precordial leads, and slurring in the right arm lead, the intrinsic deflections of these leads averaged more than 0.02 second. In no group was a greater mean intrinsic deflection than 0.031 second found.

TABLE XIV. CARDIAC RATES (BEATS PER MINUTE)

	GROUP I	GROUP II	GROUP III	GROUP IV
Range	90 to 209	125 to 209	116 to 200	100 to 179
Mean	147.9	163.3	154.8	127.1

TABLE XV. CARDIAC RHYTHM

GROUP I	GROUP II	GROUP III	GROUP IV
73% sinus rhythm 27% sinus arrhythmia (1 with ventricular ectopic beats)	62% sinus rhythm 38% sinus arrhythmia	63% sinus rhythm 37% sinus arrhythmia	11% sinus rhythm 89% sinus arrhythmia (1 with ventricular ectopic beats)

TABLE XVI. MEAN DURATION OF THE P-R INTERVAL

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R2}	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
Group I	0.10	0.10	0.10	0.09	0.09	0.10	0.09	0.10	0.10	0.10	0.10	0.10	0.09	0.09	0.09
Group II	0.10	0.10	0.09	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09	0.09	0.09	0.09
Group III	0.10	0.10	0.10	0.10	0.11	0.11	0.10	0.10	0.10	0.10	0.11	0.10	0.10	0.10	0.10
Group IV	0.10	0.11	0.10	0.09	0.11	0.11	0.11	0.11	0.12	0.11	0.12	0.11	0.11	0.11	0.11

S-T Interval.—The S-T interval was the most difficult item to measure accurately on the electrocardiograms. In many instances, especially in the right precordial leads in hearts with rapid rates, there was no apparent S-T interval, the termination of the R or S wave sloping directly up or down to form the anterior limb of the T wave (see Fig. 5). Few conclusions can be drawn from these figures except to mention that for each given individual the duration of the S-T segment in the different leads seems quite constant. Most of the S-T intervals were 0.055 to 0.065 second in duration.

Small deviations of the S-T segment of 1 mm. or less above or below the isoelectric line were found in all age groups. Among the forty-eight newborn infants, a marked depression of the S-T segment of 1.2 to 2.0 mm. below the isoelectric line was seen frequently in the precordial leads, most often in those from the right side of the precordium.

Q-T Interval.—The Q-T interval, like the S-T interval, remains nearly constant throughout the electrocardiogram of any one individual. However, wide variations are seen among the members of each age group. Because of the rapid heart rates of young children, the intervals are shorter than those seen in adult electrocardiograms. In our study, they averaged between 0.23 and 0.28 second, the longer intervals being found in the older children. The increase to 0.28 second described by Miller and Groedel[5] as being found at 4 months of age, did not occur in our series until the age of one year. In adults it has been noted that the duration of the QT interval is shorter in males than in females with the same heart rates. We found no such sex difference in our infants.

DISCUSSION

The value of such a group of measurements as this is greatly enhanced if the results are compared with those obtained on other similar groups of individuals. Only by compiling statistics for many such series can acceptable standards for

TABLE XVII. MEAN DURATION OF QRS INTERVALS

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
Group I	0.047	0.04	0.05	0.046	0.05	0.046	0.049	0.048	0.05	0.05	0.048	0.05	0.05	0.048	0.048
Group II	0.049	0.04	0.05	0.047	0.04	0.048	0.052	0.056	0.05	0.05	0.05	0.047	0.049	0.05	0.046
Group III	0.048	0.05	0.06	0.049	0.05	0.05	0.059	0.058	0.06	0.06	0.056	0.05	0.05	0.05	0.055
Group IV	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.065	0.07	0.06	0.06	0.06	0.06	0.06	0.06

TABLE XVIII. MEAN DURATION OF S-T INTERVALS

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
Group I	0.057	0.058	0.07	0.07	0.067	0.06	0.058	0.059	0.053	0.06	0.066	0.07	0.064	0.058	0.06
Group II	0.062	0.056	0.06	0.062	0.062	0.063	0.057	0.055	0.062	0.06	0.057	0.06	0.055	0.062	0.06
Group III	0.055	0.052	0.06	0.057	0.061	0.059	0.062	0.057	0.055	0.06	0.05	0.05	0.057	0.06	0.06
Group IV	0.058	0.051	0.07	0.068	0.063	0.055	0.058	0.057	0.061	0.07	0.05	0.04	0.055	0.061	0.06

TABLE XIX. MEAN DURATION OF Q-T INTERVALS

LEAD	1	2	3	AV_L	AV_F	AV_R	V_{R3}	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
Group I	0.23	0.25	0.25	0.255	0.255	0.254	0.257	0.252	0.25	0.251	0.253	0.259	0.25	0.249	0.241
Group II	0.24	0.23	0.23	0.231	0.241	0.239	0.232	0.231	0.23	0.227	0.238	0.235	0.23	0.23	0.232
Group III	0.242	0.25	0.24	0.243	0.241	0.259	0.245	0.241	0.24	0.213	0.246	0.243	0.26	0.25	0.247
Group IV	0.275	0.28	0.26	0.277	0.285	0.271	0.28	0.28	0.271	0.28	0.287	0.272	0.28	0.26	0.264

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infants and young children be obtained. The wider variations among children, as compared with adults, make it most important that a large number of children be studied. This was brought strikingly to our attention by the marked discrepancies between our measurements and those of other reliable workers.

SUMMARY AND CONCLUSIONS

The electrocardiograms of 100 normal children between the ages of 12 hours and 4 years were studied in an attempt to add to the present data accurate measurements of all components of the electrocardiogram for these ages. Forty-eight of the children were less than 8 days old.

The following conclusions may be drawn:

1. The electrocardiograms of newborn infants show the greatest variation from the normal standards for older children and adults.

2. The amplitudes of all waves of the electrocardiogram are greater in the age range studied than is considered normal for adults. Increase in amplitude is most marked in the Q wave.

3. The electric axis of the heart exhibits predominantly right deviation after birth, and during the first few months of life it changes gradually to a normal axis.

4. Vertical and semivertical positions of the heart are most common, but horizontal positions are not abnormal in newborn infants.

5. M-shaped QRS complexes in the precordial leads to the right of the sternum are not abnormal, providing the duration of the complex is normal and the second upward deflection is narrow.

6. Negative or diphasic T waves are found in Lead I and Lead II in a few normal infants.

7. Negative T waves may be found in any precordial lead in a newborn infant, and are frequently found in the right precordial leads in older infants.

8. Sinus arrhythmia is less common in the first few months of life than later in childhood.

9. The S-T interval is sometimes absent in babies with rapid heart rates, and when present may be slightly elevated or depressed. In newborn infants there may be marked depression of the S-T segment, especially in the right precordial leads.

10. There is no sex difference in the Q-T interval duration in this age group.

11. The differences between the electrocardiograms of young children and those of adults can be predicted and explained by consideration of the anatomical and physiological characteristics of the growth and development of the heart and chest after birth.

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REPORT OF TEN CASES OF POLIOMYELITIS IN INFANTS UNDER SIX MONTHS OF AGE

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POLIOMYELITIS, interestingly enough, seems to spare the infant under 6 months of age. We have been able to find only seventeen cases in infants under 6 months of age reported in the literature since 1897. Table I gives in brief a résumé of these. Undoubtedly this does not represent a true picture of the disease in this age group, but such cases are rare enough to warrant reporting them.

In the poliomyelitis epidemic of 1948 in the County of Los Angeles there were 2,973 cases seen in the Communicable Disease Unit of the Los Angeles County Hospital and only ten of these patients were under 6 months of age. Their cases are reported here.

These ten infants were admitted to the hospital between August and December, 1948. The youngest was 14 days of age and the oldest 5½ months. Four were under 3 weeks of age and eight were under 2 months. Eight of the ten were males. All those 2 months of age or younger were males. All were Caucasian. Nine were of the spinal type. Only one patient had bulbar signs. The mortality for the group was 10 per cent. This one death (Case 9) occurred in a 5½-month-old girl who was admitted on September 17 with a three-day history of fever, irritability, anorexia, weakness, and paralysis of the lower extremities. On the twentieth hospital day bronchopneumonia developed. Death intervened on Oct. 16, 1948, the twenty-sixth hospital day.

An attempt was made to ferret out any possible contact with the disease in each case. However, only two of the ten patients had known contact. One infant (Case 1), 14 days of age, developed symptoms five days after his mother manifested the disease. The second infant (Case 4), 3 weeks of age, developed poliomyelitis ten days after the onset of infection in his 5-year-old brother. The remaining eight infants had parents and siblings who were clinically well in every repect.

In reviewing presenting signs and symptoms in our ten patients, it is interesting to note that two of them had an upper respiratory infection, two had manifested irritability, five of them had fever over 101° F., five had been anorexic, and in eight of the infants weakness or paralysis had been noted prior to admission. Two of the ten infants had weakness and paralysis as the only findings. Conspicuous by their absence were: meningeal signs, convulsions, and gastrointestinal disturbances. There was a minimum of extension of the disease process after hospitalization. Attention is invited to the fact that in the seventeen cases reviewed in Table I, not one presented meningeal signs, gastrointestinal symptoms, or convulsions.

From the Communicable Disease Service of the Los Angeles County Hospital.

The highest white blood count was 26,000 and the lowest 5,250, the average 11,000. The neutrophile count varied between 36 per cent and 72 per cent. Spinal cell counts presented a low of 8 lymphocytes and a high of 330 (all lymphocytes). Two had 100 cells or more.

Treatment was essentially supportive. All received hot moist packs. Intramuscular penicillin was given to seven as a prophylaxis against secondary infection.

Neurological examination of the ten patients revealed that seven had absence of deep reflexes, one had right peripheral facial paralysis, one had absent gag reflex, and one was unable to swallow. Six had intercostal weakness and two diaphragmatic, yet only one of these patients required the respirator. When discharged from the hospital, residual involvement was as follows: five patients had paralysis of one extremity or more (right leg in two, right arm in one, left arm in two, both arms in one, and both legs in two); one patient had generalized muscle tenderness as the only involvement; one patient had scoliosis. Eight of them had some paresis, either with or without paralysis.

CASE HISTORIES

CASE 1.—G. T., a 14-day-old white male infant (first born, full term, with uneventful delivery on Oct. 5, 1948) entered the Communicable Disease Unit of the Los Angeles County Hospital on Oct. 19, 1948, with the following history:

Unexplained fever on the tenth day of life (four days prior to entry), generalized weakness, flaccid right arm, and anorexia. The latter symptoms were noted two days prior to entry.

The infant was breast fed for five days only, because the mother developed paralytic poliomyelitis. The onset of the mother's illness was two days prior to her entry into the hospital (or on the infant's third day of life). The infant remained in the original nursery until the tenth day of life. All relatives at home were in good health.

On admission to the Communicable Disease Hospital, the infant, weighing 7 pounds, appeared to be acutely ill, but in no distress. Temperature was 98.6° F. (rectal). Ear, nose, and throat examinations were normal; lungs were clear; heart was normal. Superficial and deep reflexes were hypoactive. Moro's reflex was absent. Kernig's and Brudzinski's signs were negative. The neck and back were supple. There were no meningeal signs. There was generalized weakness; both arms were flaccid.

Laboratory findings: Hemoglobin was 18.5 Gm., white blood count: 7,500 with 36 per cent polymorphonuclears. Lumbar puncture showed clear, colorless fluid with 37 cells, all lymphocytes. The Pandy was 2 plus and the sugar normal.

The baby was afebrile while hospitalized. He ate slowly, but swallowed well. When discharged to another hospital* on Nov. 2, 1948, the eighteenth day of illness, the infant showed paralysis of both upper extremities and scattered weakness of lower extremities, but no involvement of chest or diaphragm. The weight at discharge was 8 pounds.

*After the quarantine period, patients are transferred to a secondary hospital for follow-up care.

TABLE I. REVIEW OF THE LITERATURE ON POLIOMYELITIS IN INFANTS UNDER SIX MONTHS OF AGE

AUTHOR	YEAR REPORTED	AGE OF PATIENT	CONTACT	SYMPTOMS		C.S.F.	SEQUELAE
				CONVULSIONS, MENINGEAL SIGNS, G. I.	FEVER ANOREXIA PARALYSIS		
Falk[1]	1897	15 da.	None	No	Yes	None	Recovery
Guyot and Rocher[2]	1902	2 mo.	None	No	Yes	None	Paralysis
Carpenter[3]	1905	2½ mo.	None	No	Yes	None	Paralysis
Gunewardene[4]	1918	12 da.	None	No	Yes	100 cells	Recovery
Peabody and associates[5]	1912	2 wk.	?	?	?	?	?
Bruce and Moren[6]	1927	6 mo.	None	?	?	?	?
Fuks and associates[7]	1933	2 wk.	None	No	Yes	None	Recovery
Cislaglii[8]	1934	4 mo.	None	No	Yes	None	Paralysis
de Large[9]	1935	1) 15 da. 2) 5 wk.	None None	No No	No No	None None	Death Death
Alesen[10]	1939	20 da.	Yes	No	Yes	None	Paralysis
Severin[11]	1939	7 da.	No	No	Yes	Positive	Death
Gracoski and Hurmazache[12]	1940	20 da.	?	?	?	?	?
Hess and Levinson[13]	1942	4 mo.	Yes	No	Yes	276 cells	Recovery
Biermann and Piszcek[14]	1944	11 da.	Yes	No	Yes	57 cells	Death
Lubchenco and associates[15]	1944	4 mo.	?	?	?	?	?
Horn and Weidenthal[16]	1948	3 wk.	Yes	No	Yes	?	Death
Total	17 cases		4	0	11		5 deaths 4 recovery 4 paralysis

CASE 2.—W. F., an 18-day-old white male infant was admitted to the Communicable Disease Unit on Aug. 18, 1948, with a history of having manifested listlessness, anorexia, fever, and weakness of the left arm on Aug. 16, 1948. The infant had had a normal birth. There were no known contacts to any disease. Parents and one sibling were well.

The 9-pound infant, appearing acutely ill, was listless and had a temperature of 100° F. (rectal). Skin was clear. Eyes, ears, nose, and throat were normal. Lungs were clear. Heart was normal. There were no meningeal signs (Kernig's and Brudzinski's negative). The left arm was flaccid; the right leg was weak. There was questionable weakness of the right arm. Moro's reflex was absent and the right knee jerk was hypoactive.

Laboratory findings: hemoglobin was 14.0 Gm., and white blood count 14,800 with 68 per cent polymorphonuclears. Lumbar puncture revealed clear, colorless fluid with 107 cells, 90 per cent lymphocytes, a trace of Pandy, and sugar normal.

In addition to hot packs and symptomatic treatment he received penicillin 30,000 units every three hours. At the time of discharge the following were in evidence: left total scoliosis; paresis of the left arm, both legs, left intercostals and abdominals, and weakness of the left arm. There had been no respiratory difficulty at any time.

CASE 3.—R. E., an 18-day-old white male infant (first born, full term with normal uneventful delivery) entered the Communicable Disease Unit on Nov. 2, 1948, with a history of right leg weakness of three days' duration. There were no known contacts to any disease. Parents had been in good health.

On entry, he weighed 8 pounds, his temperature was 99.0° F. (rectal), pulse was 120, and respirations 28. He was well developed and well nourished and did not appear acutely ill. Skin was clear. Eye, ear, nose, and throat were normal. Lungs were clear; heart was normal. There were no meningeal signs. Ankle and knee jerks were absent bilaterally. There was weakness of the right leg. Moro's reflex was intact.

Laboratory findings were as follows: hemoglobin 16.0 Gm., and white blood count 26,000 with 54 per cent polymorphonuclears. Lumbar puncture revealed clear, colorless fluid with 8 cells, all lymphocytes, negative Pandy, and sugar normal.

Treatment consisted of symptomatic measures and penicillin 40,000 units every three hours. The infant was afebrile while hospitalized and his course was uneventful. When discharged on Nov. 15, 1948, on the thirteenth hospital day, findings were tenderness of thighs, calves, and hamstrings.

CASE 4.—F. S., a 3-week-old white male infant, entered the Communicable Disease Unit on Oct. 16, 1948, with generalized weakness and anorexia of three days' duration.

The patient was an adopted infant who came to his new parents at 5 days of age after being pronounced normal following an examination. Delivery had been normal. The infant was well until the present illness. A sibling (also adopted), 5 years of age, was admitted to this hospital on the same date (Oct.

16, 1948)) with paralytic poliomyelitis, the onset of which was on Oct. 3, 1948. The patient had been in contact with this sibling until entry.

On admission the infant, weighing 8 pounds, appeared acutely ill. His cry was weak. There was generalized weakness. Temperature was 97.0° F. (rectal), pulse rate 140, and respirations 30. There were no meningeal signs; deep reflexes were absent; there was weakness of both legs with paralysis of the right leg.

Laboratory examination revealed hemoglobin 14.0 Gm., and white blood count 8,350 with 32 per cent polynorphonuclears. Lumbar puncture showed cloudy fluid with 85 cells, all of which were lymphocytes; Pandy was negative, and sugar normal.

The infant was afebrile while hospitalized. Appetite was good. Residual weakness of all extremities persisted, and the infant was discharged on the twenty-ninth day of illness with the following: scattered weakness of all extremities, especially of left arm and right leg; slight intercostal weakness; and moderate "stretch pain" of all muscles.

CASE 5.—D. S., a 3-week-old white male infant entered the Communicable Disease Unit on Oct. 18, 1948, with paralysis of the right leg of five days' duration.

The infant had been delivered normally at term. Cry was immediate and spontaneous at birth. No abnormalities were noted during first five days of life, during which time a physician saw him three times. No weakness was noted. Parents and one sibling were well.

On admission the 9½-pound infant was crying lustily and did not appear to be ill. Temperature was 98.6° F. (rectal). There was absence of biceps and triceps reflexes bilaterally, right knee jerk and ankle jerks bilaterally. There was paralysis of the right leg and questionable weakness of the left leg.

Laboratory examination revealed hemoglobin 14.0 Gm., and white blood count 11,600 with 67 per cent polymorphonuclears. Attempts at lumbar puncture were unsuccessful.

The infant was afebrile while hospitalized. His appetite excellent. Stools were loose on Oct. 22, 1948. These became normal with symptomatic treatment. When discharged on the nineteenth day of his illness, residual findings were: paralytic right lower extremity, "stretch pain" of the neck, back, and hamstrings.

CASE 6.—W. H., a 5-week-old white male infant, entered the Communicable Disease Unit on Sept. 7, 1948, with generalized weakness for three days. There had been no fever, anorexia, or gastrointestinal disturbance. Prior to his illness, growth and development were normal. There was no known contact to any contagious disease.

On entry, physical examination revealed temperature 99.4° F. (rectal), pulse rate 128, and respirations 60. The infant weighed 9 pounds. Skin was clear. Head was symmetrical with soft fontanel. Eye, ear, nose, and throat were normal. The neck was supple. Chest had no intercostal or diaphragmatic weakness. Heart and lungs were normal. Deep and superficial reflexes were

absent. There was generalized weakness and paresis of the left arm. Moro's reflex was absent.

Laboratory report: spinal fluid was clear and colorless with 31 cells, 95 per cent lymphocytes, one plus Pandy, and sugar normal.

The patient was afebrile during the entire period in the hospital. The infant had a period of transient cyanosis on Sept. 19, 1948, when placed on his left side and was relieved by placing him on his back or right side. Chest film showed elevation of the right diaphragm. On Nov. 1, 1948, the infant was transferred to another hospital with paralysis of the right diaphragm and left arm and weakness of both legs and right arm.

CASE 7.—L. C., a 6-week-old white male infant, entered the Communicable Disease Unit on Sept. 29, 1948, having been well until the day before entry, at which time there was sudden onset of weak, feeble cry, anorexia, and weakness of the neck.

The infant had a full-term normal delivery. He developed normally. Parents and two siblings were well. There were no known contacts to any disease.

On admission the infant weighed 10 pounds and was acutely ill. Temperature was 97.8° F. (rectal). There were no meningeal signs. Right peripheral facial paralysis was apparent. Gag reflex was absent. There was paresis of the left leg.

Laboratory examination revealed a hemoglobin of 13.0 Gm., and white blood count of 16,000 with 48 per cent polymorphonuclears. Lumbar puncture showed clear, colorless fluid with 80 cells, all lymphocytes, a trace of Pandy, and normal sugar.

Treatment for bulbar spinal poliomyelitis was instituted on entry. Within twenty-four hours the infant was lethargic and required gavage feeding. He became cyanotic without oxygen, but did not require a respirator. Within seventy-two hours the infant became active, moving all extremities. He attempted to swallow but fatigued easily. On Oct. 12, 1948, he had a short episode of diarrhea which subsided with symptomatic treatment. The infant was discharged to another hospital on the thirty-seventh day of his illness with slight scattered weakness of all extremities and slight intercostal weakness; without oxygen the patient fatigued easily and became cyanotic. There was neck, back, and hamstring tightness. His weight was 10 pounds.

CASE 8.—J. W., a 2-month-old white male infant, entered the Communicable Disease Unit on Aug. 24, 1948, with a history of fever and pharyngitis five days prior to entry, and lethargy and anorexia of two days' duration.

The infant was well previous to onset. Birth weight was 8 pounds. Development was normal. A 6-year-old sibling had an unexplained fever three days prior to onset of the patient's illness. Parents were well.

On admission, the infant was acutely ill and lethargic. There was generalized weakness. Temperature was 98.2° F. (rectal), pulse rate 122, and respirations 32. There were no meningeal signs. Deep reflexes were absent. There was marked weakness of the right arm, moderate weakness of the left arm, marked weakness of both legs, and tenderness of hamstrings.

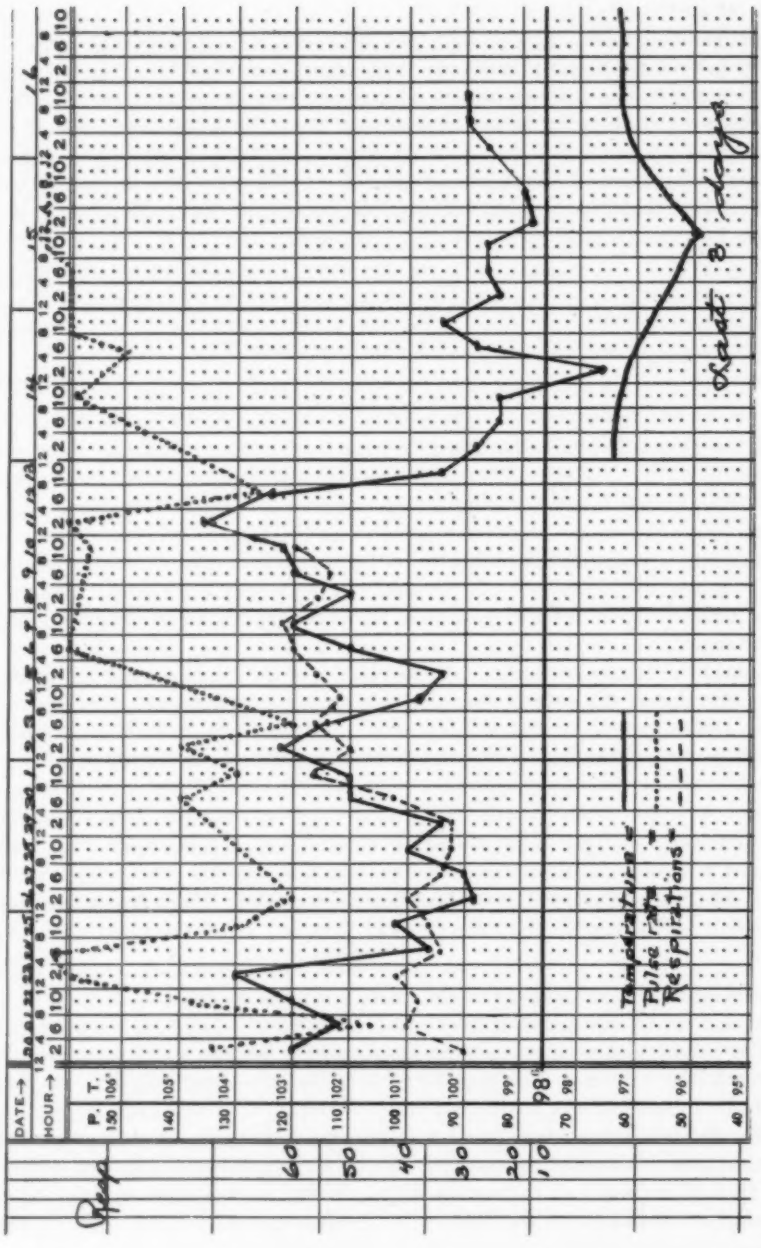

Fig. 1.—Composite graph in Case 9.

Laboratory examination revealed hemoglobin 12.5 Gm. and white blood count 5,250 with 52 per cent polynorphonuclears. Lumbar puncture was traumatic with blood-tinged fluid. The Pandy was negative and the sugar normal.

The infant was afebrile throughout the entire hospital stay. He ate well. The infant was discharged to another hospital on the nineteenth day of his illness with paralysis of right upper and both lower extremities; scattered weakness of the left upper extremity; moderate muscle tenderness; slight intercostal weakness, and moderate "stretch pain" of hamstrings, neck, and back.

CASE 9.—A. M., a 5½-month-old white female infant, entered the Communicable Disease Unit on Sept. 20, 1948, with a history of fever, irritability, anorexia, and weakness of both legs of three days' duration, with inability to move the legs for one day.

The infant was born in the Los Angeles County Hospital on April 12, 1948. Delivery was uneventful and birth weight 6 pounds. She was the second born. Growth, development, and general health were normal until the present illness. There were no known contacts with poliomyelitis or any other disease. Parents and one sibling were well.

On entry the infant weighed 14 pounds, temperature was 102.6° F. (rectal), and pulse 140. She was well-developed, well-nourished, and acutely ill but in no distress. Skin was clear. Her head was symmetrical with soft fontanel, not bulging or tense. Eye, ears, nose, and throat were normal. There was a good gag reflex. The neck was supple and the chest symmetrical without evidence of respiratory weakness. Lungs were resonant and clear and heart normal. Liver, spleen, and kidneys were not palpated. There was a paralyzed right leg and paretic left leg. No muscle tenderness or bulbar signs. Absent ankle and knee jerks bilaterally.

Laboratory findings: hemoglobin was 12.0 Gm., and white blood count 11,550 with 72 per cent polymorphonuclears. Lumbar puncture revealed clear, colorless fluid with 330 cells, 95 per cent of which were lymphocytes, Pandy 2-plus, and sugar normal.

Treatment started on entry consisted of hot packs, sodium chloride 0.5 Gm. daily, stimulants, penicillin 20,000 units every three hours, respirator, Intocostrin 0.5 c.c. intramuscularly given because of incoordination of patient's breathing with the respirator, sulfadiazine, 0.12 Gm. every three hours for six days.

The infant was febrile throughout her entire hospital course. On Sept. 22, 1948, fever was 102° F. (rectal) and pulse 136. Respirations were largely diaphragmatic. Weakness of both legs was unchanged. There were no bulbar signs. On Oct. 11, 1948, there was increased respiratory distress, râles were heard throughout the chest, and the patient was cyanotic. Chest film showed diffuse bronchopneumonia. The infant was placed in a respirator. White blood count was 41,100 with 90 per cent polymorphonuclears. Intocostrin synchronized the patient's breathing with the movements of the respirator.

On Oct. 16, 1948, the infant suddenly became pale and expired. During the twenty-four hours previous to death, it became rapidly and progressively

TABLE I*

CASE NO.	AGE	SEX	HOSP. DAYS	CONTACT	COMPLAINTS	REFLEXES	RESIDUAL N. M. †		
							ARMS	LEGS	BACKBONES
1	14 days	M	13	Yes	Fever—4 days; anorexia; general w.; w. R. arm	h. deep; h. superficial; h. Moro	p.	w.	
2	18 days	M	13	None	Irritability; abd. pain; fever; listlessness (2 days)	h. R. knee jerks; h. Moro	p.L. w.R.	p.	p.
3	18 days	M	13	None	w. R. leg (3 days)	ab. ankle; ab. knee jerks; w. R. leg			
4	21 days	M	26	Yes	Anorexia; general w. (3 days)	ab. deep; w. legs; w. neck			
5	21 days	M	14	None	p. R. leg (5 days)	ab. biceps; ab. triceps; ab. ankle; ab. knee jerks		p.R.	T.
6	5 weeks	M	55	None	General w. (3 days)	ab. superficial; ab. deep; p. L. arm	p.L. w.R.	w.	
7	6 weeks	M	36	None	Weak cry; anorexia; weak neck (1 day)	ab. gag reflex; p. R. facial; w. L. leg			
8	2 mo.	M	14	None	URI; fever (5 days); lethargy; anorexia (2 days)	ab. knee; ab. ankle jerks	p.R.	p.R. p.L.	
9	5½ mo.	F	26	None	Fever; irritability; anorexia; w. of legs (3 days); p. legs (1 day)	ab. knee; ab. ankle jerks; p. R. leg			
10	5½ mo.	F	15	None	URI—2 weeks; w. cry; w. neck (3 days); nasal voice; w. R. arm (1 day)	ab. superficial; h. deep	w.R.	w.L.	

ab. indicates absence of; *h.* indicates hypoactive; *p.* indicates paralysis; *T.* indicates tightness of *URI* indicates upper respiratory infection; *w.* indicates weakness; *R.* and *L.* indicate right and left.

†*N. M. F.* indicates Neuromuscular findings.

worse. Autopsy was not permitted. Death was believed to be due to fulminating bilateral bronchopneumonia. (Composite graph of infant's temperature during stay in hospital is shown in Fig. 1.)

CASE 10.—L. G., a 5½-month-old white female infant, entered the Communicable Disease Unit on Dec. 9, 1948, with a history of an upper respiratory infection of two weeks' duration; weakness of neck, and weak cry three days'; and weakness of right arm and both legs on the day of entry. Previously the infant had been well; development had been normal. Her parents and one sibling were well.

The infant weighed 13 pounds, was acutely ill, listless, and pale, with a temperature of 100.6° F. (rectal), pulse rate 140, and respirations 28. Meningeal signs were absent. The infant was unable to hold her head up. Breathing was abdominal. There was questionable abdominal weakness. There was weakness of both the left leg and right arm with slight generalized weakness. Voice was nasal with no swallowing difficulty.

TABLE II*

R. M. F.†					LABORATORY WORK				
					SPINAL FLUID		BLOOD COUNT		POLYS.
ABDS.	INTER-COSTALS	DIA-PHRAGM	NECK	MISCELLANEOUS	CELLS	CULTURE	HB.	WBC	(%)
					37	0	18.5	7,500	36
p.	p.L.			L. scoliosis	107	0	14.0	14,800	60
				T. of all muscles	8	0	16.0	26,000	54
	w.			General w.; T. thighs	85	0	14.0	8,350	32
			T.		None obtained		14.0	11,600	
		p.R.			31	0		None	
	w.			General w.	80	0	13.0	16,000	48
				General w.; T. hamstring	90	0	12.5	5,250	52
				DEATH	330	0	12.0	11,550	72
	w.			T. general	49	0	10.5	9,500	64

Laboratory examination revealed hemoglobin 10.5 Gm. and white blood count 9,500 with 64 per cent polymorphonuclears. Lumbar puncture showed clear, colorless fluid with 49 cells, 40 per cent of which were lymphocytes, Pandy 1 plus, and sugar normal.

Therapy for spinal poliomyelitis was begun on entry and a whole blood transfusion of 100 c.c. was given. The infant ate well. She became afebrile after ninety-six hours. Respirations were definitely diaphragmatic. The infant was discharged on the eighteenth day of her illness with considerable tenderness in all muscles, scattered weakness in the right arm and left leg, marked intercostal weakness, and moderate "stretch pain" in neck, back, and hamstrings.

SUMMARY

Ten infants under 6 months of age with poliomyelitis are here presented. There was one death, giving the group a 10 per cent mortality. In two cases there was a history of contact with paralytic poliomyelitis prior to the onset of symptoms. Five of the patients had paralysis of one extremity or more, and eight of them had residual weakness. None of the patients manifested meningeal signs, gastrointestinal disturbances, or convulsions. There appeared to be a minimum of extension of the disease process after hospitalization.

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THE INCIDENCE OF MONGOLOID IMBECILITY IN THE NEWBORN INFANT

A Ten-Year Study Covering 27,931 Live Births

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THE TRUE incidence of Mongoloid imbecility in the general population has never been ascertained with certainty. Since the condition was first described by Down,[1] there have been a number of reports in which attempts have been made to estimate the incidence of the affliction. Estimates have been made on the basis of the proportion of Mongoloids to other feeble-minded individuals in an institution[2] or to the general population in a large general outpatient clinic.[3] Both of these methods have obvious disadvantages. The ideal situation in which to study the incidence of an anomaly such as mongolism is in the newborn nursery. This has been done by Beidleman,[4] who took a sampling of 14,000 liveborn infants at the Boston Lying-In Hospital. There were forty-eight Mongoloid imbeciles, or an incidence of 3.4 per 1,000 live births.

In order to throw more light on the exact incidence of mongolism and to determine whether or not the high figure reported by Beidleman pertains to other sections of the country and to other races and economic strata, we have studied the incidence of the condition as it has been recognized in the obstetric nurseries of the Gallinger Municipal Hospital.

The subjects of this study include 27,931 consecutive infants born alive in this hospital from Jan. 1, 1939, to Dec. 31, 1948. No infant born alive during this period has been excluded. The diagnosis has been based on the composite clinical picture of mongolism, which is well recognized. All diagnoses have been checked by members of the senior staff of pediatrists. The accuracy of the diagnosis is attested by the facts that among infants who have returned to this hospital for follow-up, no diagnosis of mongolism has been made subsequently on any infant born in the hospital in whom it was not made at birth, and no diagnosis made at birth has been reversed on reexamination.

Table I shows the total births in the hospital by race and sex with the incidence of mongolism in each group. Among the 27,931 liveborn infants, a total of thirty-two Mongoloid imbeciles were diagnosed at birth. This gives an incidence of 1.15 per thousand, or a ratio of one Mongoloid imbecile to 873 liveborn infants. There were 25,026 Negroes and 2,905 white infants. Among the 25,026 Negro infants there were diagnosed twenty-nine Mongoloid imbeciles, an incidence of 1.16 per thousand, or one to 863; among the 2,905 white births there were found three Mongolian imbeciles, an incidence of 1.03 per thousand, or one to 968. This data would seem to indicate little difference in the relative frequency of mongolism in one race as compared to another. Likewise in relation to sex, there seems to be no significant difference as evidenced by a total incidence in female infants of one to 922 and in male infants, one to 830. It is of interest to note that ten, or 31 per cent of our Mongoloid imbeciles, were prematurely born infants, as compared to 43 per cent prematurely born infants in

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the series reported by Beidleman.[4] During the ten-year period there have been 3,543 premature infants born in the hospital, a total of 12.6 per cent of all births. Among these there have been ten with mongolism, an incidence of 2.8 per thousand, or a ratio of one to 354. This is shown in Table II.

TABLE I. THE INCIDENCE OF MONGOLOID IMBECILES ACCORDING TO RACE AND SEX

	LIVE BIRTHS	MONGOLOID IMBECILES	RATIO OF MONGOLOID IMBECILES TO TOTAL BIRTHS
Total white infants	2,905	3	1:968
Male infants	1,512	2	1:756
Female infants	1,393	1	1:1,393
Total Negro infants	25,026	29	1:863
Male infants	12,595	15	1:840
Female infants	12,431	14	1:888
Total male infants	14,107	17	1:830
Total female infants	13,824	15	1:922
Total infants	27,931	32	1:873

TABLE II. RATIO OF MONGOLOID IMBECILES FOR FULL-TERM AND PREMATURE INFANTS

	LIVE BIRTHS	MONGOLOID IMBECILES	RATIO OF MONGOLOID IMBECILES TO TOTAL BIRTHS
Full-term infants	24,388	22	1:1,108
Premature infants	3,543	10	1:354
Total infants	27,931	32	1:873

The incidence of mongolism as found in this study (1.15 per thousand or 1:873) is much less than that reported by Beidleman (3.4 per thousand or 1:292). This is not accounted for by the race of the patients, since we have found mongolism to be as prevalent in Negro as in white infants. It is unlikely that the lower economic status of our patients can account for the discrepancy. Further studies of this type are needed before the precise incidence of this defect can be determined.

SUMMARY AND CONCLUSIONS

A study of the incidence of Mongoloid imbecility in a newborn nursery during a ten-year period has been made. There were thirty-two Mongoloid imbeciles among 27,931 liveborn infants, an incidence of 1.15 per thousand, or a ratio of one Mongoloid imbecile to 873 liveborn infants. There was no significant difference in incidence according to race or the sex of the infant. There was, however, a marked increase in the frequency among prematurely born infants (1:354) as compared to infants born at term (1:1,108).

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Case Reports

PNEUMOTHORAX IN THE NEWBORN INFANT

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UNTIL recently spontaneous pneumothorax in the newborn period was considered quite rare. Ruge[1] in 1878 reported the first case in an infant following breech delivery. By 1930 only five cases had appeared in the literature; however, since that time it has come to be recognized that pneumothorax is not an unusual cause for respiratory distress and cyanosis in the newborn infant.

We have recently studied a case of bilateral pneumothorax in a 4-day-old infant born by cesarean section. In addition to presenting this case, it is our purpose to call attention to a medical emergency that oftentimes goes unrecognized, and to review the current knowledge concerning pathogenesis and management.

CASE HISTORY

Baby girl P. was born at Colorado General Hospital at 8:15 A.M. on May 28, 1949, by cesarean section approximately one month before the expected date of confinement. The pregnancy was complicated by toxemia manifested by headache, albuminuria, and progressive elevation of blood pressure. The complication was considered indication for early delivery of the infant by operative means.

At birth the baby weighed 4 pounds, 13½ ounces and appeared to be perfectly normal. Respirations and cry were spontaneous and her color was good. The pharynx was suctioned with a soft rubber catheter, but no intratracheal or positive pressure oxygen was given.

Prelacteal feedings of glucose water were started twelve hours after birth and the second day she was taken to the breast. Sucking was normally vigorous until the 6 P.M. feeding on June 1, the fourth day of life, when she seemed somewhat lethargic and refused to nurse. At the 10 P.M. feeding she was even more listless and still declined to feed. About the same time she became mildly cyanotic and oxygen therapy was started. At 1 A.M., June 2, respirations were observed to be gasping in character and the cyanosis was intense. Physical examination still revealed no abnormal pulmonary findings. She continued to be cyanotic throughout the night, but her respirations improved and by 8 A.M. her condition seemed considerably better. A chest x-ray taken at 11 A.M. on June 2 disclosed a bilateral pneumothorax (Fig. 1). Because the infant's condition seemed to be improving, aspiration was not thought advisable. A film taken five hours later (Fig. 2) showed complete absorption of air on the right side, but persistence of the pneumothorax on the left. Occasional bouts of cyanosis were noted the evening of June 2, despite continuous oxygen and hourly carbon dioxide inhalations. Intramuscular penicillin was used for its prophylactic effect. An x-ray of the chest taken on June 3 still showed incomplete expansion of the left lung with a definite mantle of pneumothorax. She had one minor bout of

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cyanosis on June 3, following which she was symptom-free. A repeat x-ray film made on June 6 disclosed both lung fields to be normal in appearance and fully expanded, with all evidence of the previously existing bilateral pneumothorax completely obliterated (Fig. 3).

Fig. 1.

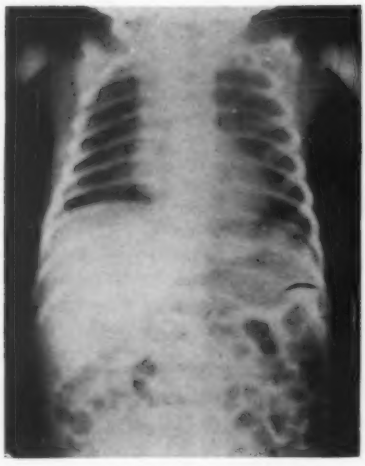

Fig. 2.

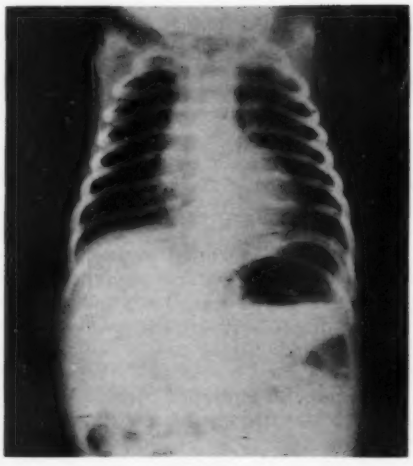

Fig. 3.

Fig. 1.—Chest x-ray taken on the fourth day of life demonstrates bilateral pneumothorax.

Fig. 2.—Repeat x-ray film taken five hours later shows absorption of the mantle of air on the right side, but persistence of the pneumothorax on the left.

Fig. 3.—Chest x-ray made on the ninth day reveals normally expanded lungs.

Throughout the illness the infant took formula feedings well, and on June 7 she was restarted on breast feedings with supplement feedings of Alacta formula. She was discharged on the twelfth day of life weighing 4 pounds, 9 ounces. The discharge examination was well within the limits of normal.

DISCUSSION

In a series of 702 consecutive x-ray examinations of newborn infants from 1927 to 1929, Davis and Stephens[2] found six cases of pneumothorax, an incidence of less than 1 per cent. DeCosta,[3] in an excellent review in 1939, could find only sixty-seven cases recorded in the newborn period, forty-six of these having occurred within the first ten days of life. Only six cases were bilateral and three of these were alternating in character. One case of simultaneous bilateral pneumothorax in DeCosta's series occurred at one month. Rothman[4] has reported a case of bilateral pneumothorax in a 3,660 gram infant following delivery by cesarean section. Cyanosis was present at birth and diagnosis was confirmed roentgenographically at 26 hours. Repeat x-ray films taken at the age of 4 days showed complete clearing. Holz[5] reported a 2,100 gram baby delivered spontaneously who developed cyanosis and dyspnea at 6 hours with x-ray evidence of bilateral pneumothorax obtained on the second day. Recovery was complete. A third case of bilateral pneumothorax occurring in the neonatal period was reported by Deissler.[6] The infant was delivered by forceps and was cyanotic from birth. Death supervened and at post-mortem examination bilateral pneumothorax associated with rupture of emphysematous blebs was demonstrated. Even though pneumothorax in the newborn period is more frequent than formerly supposed, bilateral pneumothorax in a 4-day-old premature infant is still unusual.

DeCosta[3] has classified neonatal pneumothorax under two headings: the first, pneumothorax abrupta, usually occurs at birth and is manifested by dyspnea, a weak cry, and cyanosis. The distress is usually severe and the symptoms progress rapidly. The second type, which he has termed pneumothorax lenta, is characterized by mild symptoms and an insidious onset occurring hours or days after birth. Physical signs are often lacking. Our case falls into this second group. The symptoms appeared on the fourth day of the infant's life and developed to a maximum intensity over an eight-hour period. Physical signs were entirely absent. With the more abrupt onset, a hyperresonance of the involved hemithorax and a corresponding diminution of breath sounds, often associated with demonstrable shift in the mediastinum, suggests the diagnosis. Occasionally subcutaneous emphysema in the neck may be an associated finding.

The etiology of this condition is varied and is oftentimes in doubt. Congenital anomalies can occasionally be established as the probable underlying cause. Weiner[7] reported a case diagnosed as pneumothorax on the fourteenth day of life. The infant died at 4½ months of age and was found to have a bronchopleural fistula. Giant lung cysts may rupture and produce pneumothorax. Aplasia of the lung is a congenital defect capable of producing pneumothorax.

A second accepted cause is infection, but this is more likely to occur beyond the newborn period. Pneumothorax may complicate pneumonia, particularly when the hemolytic *Staphylococcus aureus* is the etiologic agent. Glaser and Landau[8] reported pneumothorax in a 20-day-old infant who subsequently died on the twenty-fifth day of life. At autopsy a 3 by 8 mm. abscess was found in the lateral aspect of the lower lobe of the left lung. Weiner[7] also reported a case of pneumothorax due to rupture of an abscess in the upper lobe on the right diagnosed in a patient 3 weeks of age. It was postulated that the abscess was secondary to an aspiration pneumonitis acquired at or shortly after birth.

A third and probably uncommon cause is direct trauma to the chest as might be acquired in birth injury or from unskillful artificial respiration. Fracture of a rib or clavicle with perforation of the pleura may occur. Strongin[9] has reported pneumothorax in a 4,535 gram infant with an associated Erb's palsy. Delivery was by manual rotation and difficult midforceps extraction.

The fourth and probably the principal cause for pneumothorax in the newborn infant is related to the pneumodynamics of the alveolar sacs. Though the exact mechanism is unknown, there is incontrovertible evidence that overdistention is an important factor. It was formerly believed that increased pressure in the lungs caused rupture of peripheral emphysematous blebs into the pleural cavities with development of pneumothorax. Autopsy findings have failed to substantiate this. Ruge,[1] in the first reported case, did find a tear in the pleura, but since then gross tears or rupture of emphysematous blebs have been found infrequently. Even microscopic examination fails for the most part to account for the leakage of air. Rupture of a single peripheral emphysematous bleb certainly doesn't explain the cases of bilateral pneumothorax. In 1733 Hales[10] showed that hyperinflation of the lungs caused air to escape into the pleural spaces without gross dilatation or tear of alveoli. Ogawa[11] in 1922 described the existence of pores between the alveoli in animals and Macklin[12] demonstrated similar pores in the human lung. Van Allen[13] showed that although these pores are normally closed, they may open with increased intra-alveolar pressure. Macklin[14] also demonstrated that increased tension within the alveoli caused emphysema and ultimate rupture of the alveoli into the perivascular sheaths and a spread of air into the mediastinum. DeCosta[3] showed that pressures as low as 24 cm. of water produce bullous mediastinal emphysema in some dogs. Once air has reached the mediastinum it may rupture into one or both pleural cavities, may extend into the neck or axilla or into the retroperitoneal space and peritoneal cavity. This explains more satisfactorily the occasional appearance of bilateral pneumothorax and the paucity of post-mortem findings.

A case reported by Silver[15] seems to illustrate the above method of development of pneumothorax. A 5 pound, 7½ ounce infant was delivered without undue incident and appeared active and vigorous at birth. Four hours later cyanosis developed and persisted intermittently. The second day of life an x-ray film of the chest was taken and showed emphysema of the entire right lung with widening of the interspaces. The infant was bronchoscoped with no immediate change in the condition. The following day shock suddenly intervened and an x-ray film taken at that time disclosed a massive right pneumothorax. The baby died on the fourth day and at autopsy no tearing of the pleura or rupture of the alveoli could be found. It is likely that overdistention of the lung resulted in infiltration of air along the perivascular spaces into the mediastinum, escaping from there into the pleural cavity.

Overdistention of the alveoli may be produced in many ways. Coughing may suddenly dilate the alveoli and smaller bronchioles. Obstruction of the respiratory tract with mucus or aspirated vermix caseosa may cause distention by a ball-valve action. Extrinsic obstruction of the respiratory tract as may be seen with a vascular ring, an exceptionally enlarged thymus, and in rare cases a cord tightly wrapped around the neck may be responsible. Positive pressure oxygen or oxygen delivered through a tracheal catheter may overdistend the alveoli. Emmert[16] reported a case of pneumothorax which occurred after mouth-to-mouth resuscitation of a newborn infant. Even normal respiratory efforts, especially those during the first hours of life, may dilate alveoli excessively and perhaps contribute to the perivascular spread of air. Intracranial hemorrhage or congenital heart disease may accentuate respiratory excursions and thereby contribute to increased alveolar tension. DeCosta[3] found a marked variation in the

pressure required to produce mediastinal emphysema in dogs. In some of his animals it was produced by 24 cm. of water; other dogs survived pressures of 40 cm. without gross effect. Individual variation in the lung tissue must play an important part in the development of pneumothorax. Hermann[17] has shown that pressures of 12 to 20 cm. of water are required to expand the newborn infant's lung. Once expansion has taken place, the same lungs could be expanded with pressures of 3 to 9 cm. of water. Two factors resist inflation of the newborn infant's lung: namely, cohesion of the moist surfaces of the bronchial and alveolar system of the fetal lungs; and, resistance of the elastic tissue and smooth muscle of the pulmonary parenchyma. Once these initial resistances have been overcome, distention of the alveoli is accomplished with greater ease. Smith[18] measured negative pressure produced by the newborn infant inspiring against a partial obstruction. He found that most infants on crying attained negative pressures of minus 40 cm. of water. Premature infants less than 5 pounds in weight attained the same minus 40 cm. of water in all but three out of thirteen cases. Correlation seemed to exist between the activity of the infant and the degree of negative pressure; i.e., increased activity resulted in greater inspiratory effort. With this degree of pressure transmitted to the alveoli in the newborn infant, overdistention might reasonably be expected to be a rather common occurrence. Variation in the ability of the lung tissue to withstand this distention probably explains why only a few infants develop pneumothorax. Since pressures within the respiratory tract of the premature infant are approximately the same as in a full-term infant, it follows that the immature lung should predispose to the development of pneumothorax. DeCosta[3] in his review of the literature, however, listed only seven cases of pneumothorax in premature infants out of a total of sixty-seven cases.

X-ray interpretation usually affords no difficulty, but occasionally a diaphragmatic hernia or giant congenital lung cyst must be considered.

The prognosis depends largely upon the severity of the symptoms and rapidity of their onset. It is poor in those developing pneumothorax at or shortly after birth. A 42 per cent mortality was found in this group by DeCosta.[3] In those cases in which the infant developed cyanosis and dyspnea insidiously, usually after the first day of life, only two of thirty-four died; both of these were complicated by cerebral hemorrhage.

The treatment of choice in those patients developing pneumothorax late is usually conservative; i.e., oxygen, carbon-dioxide inhalations, and prophylactic penicillin. If the pneumothorax is bilateral and so extensive that it causes serious respiratory embarrassment, aspiration of the entrapped air is indicated. In the experience of many authors a single aspiration suffices to permanently eliminate the pneumothorax. Collapse of the lung by the pneumothorax may result in sealing off of the perivascular spaces so that further leakage is prevented. It has also been pointed out by Hermann[17] that the first inspiratory efforts are forceful and that once the lung has been inflated much less pressure is required for re-expansion.

When the respiratory distress increases rapidly, death from tension pneumothorax may result. In such cases the infants are benefited by continuous underwater drainage. Repeated aspiration with a needle is indicated until some method of maintaining constant negative pressure in the involved pleural space can be established.

Although pneumothorax in the newborn infant is not a common finding, it occurs often enough that it merits consideration when an infant develops cyanosis and dyspnea shortly after birth. Since physical signs are often absent, x-ray may be the only reliable means of diagnosis. Recognition of the condition may be lifesaving in those infants requiring aspiration.

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ICHTHYOSIS FETALIS GRAVIS IN TWO SUCCESSIVE PREGNANCIES

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ICHTHYOSIS fetalis is a rare congenital disease of the skin of undetermined etiology, characterized by a thick platelike epidermis, separated by fissures, which covers the entire surface of the body, and which gives the fetus a monstrous look.

Although some authors[2, 3, 6] have suggested more comprehensive names, such as "harlequin fetus," "keratosis universalis congenita," these have not been generally accepted and the designation of ichthyosis fetalis persists.

Ormsby gives a collective review of some cases reported in the United States. In Chile similar cases have been reported by Gantes,[2] and Socías,[3] and in Argentine by Gavioli,[5] and Echavarría.[4]

The following two cases are reported because this condition is extremely rare and these infants were born in two successive pregnancies.

CASE 1.—S. R. D., 37 years of age, was admitted to the Maternity Ward of the A. C. Sanhueza Hospital on Sept. 14, 1947. She had a history of ten previous pregnancies, including three abortions at the second and third months of gestation. Maternal history was negative for TBC and syphilis. There was no history for infectious disease. Kahn reaction was negative on several occasions.

She was hospitalized in her second month of gestation for some vaginal bleeding. Recovery was prompt. During the rest of her pregnancy she was extremely undernourished because of her poor economic situation. Her meals consisted mainly of coffee, bread, soups, and occasional fruits; they were completely lacking in milk, meat, or eggs.

She worked in a home laundry until the last day of gestation. Delivery was normal and spontaneous.

A premature female baby was born Sept. 15, 1947. No asphyxia or cyanosis was present. The birth weight was 2,500 grams and body length at birth measured 47 cm. (Fig. 1).

The body was covered with large flakes of thick, whitish-yellow corneous epidermis with free edges, separated by fissures that partially involved the corium. The head was also covered with these corneus folds, obstructing normal development of the ears, nose, mouth, and eyes. No fontanel was palpated. Normal hair was present only in the parietal and occipital zone. On the face a gross bilateral ectropion covered the eyes. Nasal development was wanting. The mouth was wide open, presenting the gingival structures, and resembling a "clown's mouth." Physical examination of the chest revealed clear lungs with normal heart auscultation. Abdominal organs were normal. In the upper extremities were observed small clawlike hands with abnormal development. In the lower extremities there were clubfeet and syndactilia.

The infant was dressed with sterile gauze, sustained on oxygen and the routine care for premature babies. The general condition gradually became worse and the infant died forty-eight hours later.

A complete blood count revealed 6,000,000 red blood cells with 19 per cent erythroblasts and 90 per cent hemoglobin, leucocyte count of 13,400 with 60 per

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cent neutrophiles, 30 per cent lymphocytes, and 10 per cent monocytes. The infant's blood was found to be O-Rh positive, and her mother's blood O-Rh positive. Kahn reaction was negative.

Autopsy Observations.—A post-mortem study was made by Dr. J. Vargas.* No abnormalities were found in the brain, lungs, heart, liver, spleen, kidney, large or small intestine. Microscopic examination of the skin revealed that the epidermis was greatly hypertrophied, especially the stratum corneum, which was greatly thickened. The horny matter of this layer was arranged in fascicles like undulatory waves. In some regions they grew concentrically leaving a clear space in the center. Not all the hypertrophied stratum corenum was constituted exclusively of these horny fascicles; in some parts they shared with thin layers of clear cells resembling the stratum lucidum cells. The dermis revealed a dense, elastic tissue with a papillary layer arranged in an irregular form, forming a sinuous border with the epidermis. In some regions we found small papillae beside larger ones.

Fig. 1.—Anterior view of premature female baby. Case 1.

CASE 2.—In 1948, the mother again became pregnant. During this pregnancy she suffered from edema of her legs. She was undernourished and worked hard in a home laundry until the last moments.

She was admitted at term on Sept. 12, 1948, in labor, at the Maternity Ward of the "Hospital del Salvador." Delivery was spontaneous and normal. The infant, a premature male baby, weighed 2,020 grams, and his physical examination was very similar to the infant in the first case reported. (Fig. 2.) The body was covered with a thick corneous epidermis, giving the baby a monstrous look. This material was more exaggerated around the face, scalp, abdomen, and extremities. In his face, the eyes were prominent due to a bilateral ectropion. The mouth was wide open, showing all the gingival structures. The lung were clear and the heart sounds normal. The spleen was not palpable and the edge of the liver was at the costal margin. There was edema and also deformities in the lower extremities.

The infant's general condition seemed poor. Respiration was weak and irregular after it was established. He was placed in an incubator and given oxygen, but he died twelve hours later.

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Autopsy Observations.—An autopsy was performed by Dr. J. Vargas and the principal observations were very similar to those in Case 1. The histologic studies of the skin indicated that the chief changes were in the epidermis, especially in the stratum corneum, which was greatly hypertrophied. Microscopic

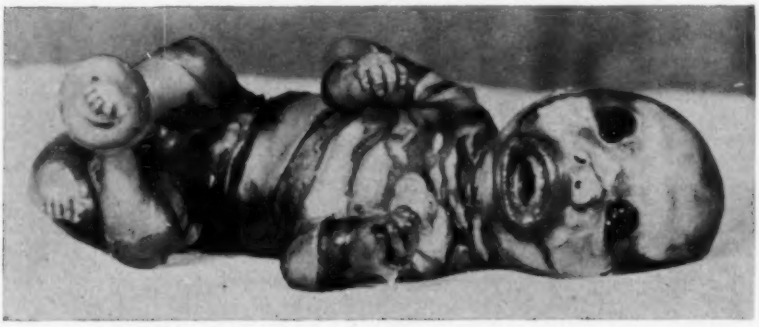

Fig. 2.—Anterior view of premature male baby, Case 2.

Fig. 3.—Microscopic section of the skin showing the great proliferation of the stratum corneum.

observations of the other organs were as follows: The liver was moderately congested. Aside from numerous areas of focal erythropoiesis, there were no notable observations. The adrenal glands showed only congestion. Thymus and thyroid were normal. No abnormalities were found in the brain, lungs, heart, or kidney. (Fig. 3.)

COMMENTS

The occurrence of ichthyosis fetalis has been divided into three clinical types: gravis, medium, and benign. The gravis type, which we have described, is incompatible with life and is only present in premature infants. The skin is represented by a thick, horny cuirass, resembling plates of armor, not compatible with growth and normal development. Most of the abnormalities described in the extremities, ears, mouth, eyes, etc., are produced by this anomaly of the skin. Nursing is very difficult and death usually takes place within the first hours or days.

The etiology is unknown, although endocrine and vitamin disturbance, syphilis, alcoholism, etc., have all been suggested as possible causes. The occurrence of more than a single case in the same family is not rare. In our cases there was a family tendency to ichtyosis fetalis in two successive pregnancies. Nevertheless, overwork and denutrition were also present.

From the histopathologic study of the skin, the most conspicuous feature was the gross proliferation and keratinization of the epithelial structure. No other pathologic findings were demonstrable on post-mortem examination.

Our study confirms the idea that the cause of ichthyosis seems to be a local anomaly of the nutrition of the skin, especially involving the epidermic layers.

Treatment is only symptomatic, skin protection against infections, and all the routine measures used in premature infants. Use of glandular extracts has been reported in cases, with doubtful results.

SUMMARY

Two fatal instances of premature infants with ichthyosis fetalis of gravis type in two successive pregnancies are reported. In each case the skin was represented by a thick horny cuirass resembling plates of armor, not compatible with normal growth and development.

Familial tendency, denutrition, and overwork during gestation are mentioned. Histopathologic study revealed a great proliferation and keratinization of the epithelial structures.

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LOEFFLER'S SYNDROME WITH SKIN MANIFESTATIONS

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IN 1932 and again in 1936 Loeffler described a syndrome which is now known by his name.[1] The chief features are transitory pulmonary infiltrations and associated eosinophilia. The clinical course has been very mild in the majority of cases, even though marked pulmonary involvement may be seen in the roentgenograms.

Since the first report of this syndrome, many cases have been reported of variable duration and severity. Serra[2] has reported a case that had been under observation for a period of thirty-two months, during which time there were four "attacks," the last of which had been present for twenty-three months at the time of his writing. Because of the variability of the clinical picture and the pulmonary findings as shown by x-ray studies, Kartagener[3] has pointed out that three different types can be demonstrated: first, the Loeffler type, which has transient pulmonary infiltrations with eosinophilia; second, the type described by Löhr and Léon-Kindberg[3] which has, in addition to pulmonary infiltration and eosinophilia, severe acute symptoms and a protracted course; and third, the type described by Kartagener himself, in which there is chronicity with mild symptoms. To our knowledge there has been only one previous report of a case of Loeffler's syndrome with a skin rash.[4]

Although the exact etiology has not been agreed upon, the consensus appears to be that the syndrome is due to an allergic response to one or more allergens. Alpher[5] has pointed out that the allergic factor may be either intrinsic or extrinsic. Intestinal parasites, tuberculosis, brucellosis, and amebiasis were mentioned under the latter group; sulfonamides and plant pollen, such as privet and Convallaria (Europe), were listed under the former. Wright and Gold[6] have reported twenty-six cases which they believed to be the result of an allergic response to creeping eruption. Falk and Newcomer[7] have recently reported two cases occurring after injections of penicillin in oil and wax; the wax was considered to be the responsible allergen.

Due to the benign course, there are few reported pathologic studies. In 1942 von Meyenburg[8] reported the post-mortem findings in four cases. The primary cause of death in three of these was accidental, and the fourth patient died from traumatic tetanus. Macroscopically, he found that the foci are not characteristic and that they have the appearance of bronchopneumonia or infarctions. A serous exudate is present in the aveoli with a variable amount of fibrin, and occasionally early organization may be present. The cells in the exudate consist mainly of eosinophiles (70 to 100 per cent), with the remainder being alveolar cells, neutrophilic leucocytes, lymphocytes, and plasma cells. Sections revealed, in all but one case, giant cells of varying shapes which were different from Langhans' giant cells. None of the sections contained tubercle bacilli. In 1945 Bayley, Lindberg, and Baggenstoss[9] reported the pathologic findings in one case. The histologic appearance was that of an unusual type of organized pneumonia containing a very great number of eosinophilic leucocytes. Focal, atypical, tuberclelike lesions were found in some parts of the pneumonic process, but tubercle bacilli could not be demonstrated in any of the sections.

The treatment has been mainly symptomatic, and some cases are so mild that none is indicated. Any underlying pathologic condition should receive appro-

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priate therapy. Since allergy apparently plays a role in the etiology, it would not seem amiss to prescribe one of the antihistaminic drugs now available.

CASE REPORT

F. J., a 2-year-old white male child, was admitted to the pediatric ward of St. Joseph's Hospital on May 27, 1949, because of a rash and fever. A low-grade fever was present for several nights prior to admission, and on the day before admission a rash had appeared on the face, neck, trunk, and feet. This eruption was described as being red and blotchy in character for the most part, with some of the individual lesions resembling nettle rash which did not respond to adrenaline. On the day of admission, the lesions on the abdomen had become bluish in appearance.

The past history revealed that the child had been admitted to the Tennessee Children's Home, an orphanage, on March 23, 1949, at which time he had rhinitis and otitis media. Because of a mild anemia, he had been placed on iron therapy. No family history or other past history was available.

Physical examination on admission revealed a temperature of 104° F. a pulse of 92, and a respiratory rate of 20. The general appearance was that of a well-developed and well-nourished 2-year-old boy who appeared acutely ill. Examination of the skin revealed irregularly shaped, erythematous, macular lesions on the face, neck, trunk, and dorsal surface of the feet, with those on the lower abdomen having a bluish tinge. The remainder of the physical examination was essentially normal except for minimal injection of the right membrana tympani.

X-ray Studies.—X-rays were taken first on May 28. They showed patchy areas of consolidation in both cardiophrenic angles, with no evidence of tuberculosis. The diagnosis was a bilateral bronchopneumonia. X-rays taken on June 6 revealed a considerable increase in the size and density of both hilar shadows and considerable peribronchial infiltration throughout both lung fields. X-rays taken on June 15 showed evidence of further increase in the infiltration compared to the two previous examinations. X-rays taken on June 27 showed that the resolution was practically complete with very slight residual haziness in the right cardiophrenic angle.

Laboratory Studies.—

The urine was normal and blood Kahn was negative. The platetlet count was 340,200 per cubic millimeter. First and second strength PPD were negative. Stool examination was negative for ova and parasites.

TABLE I

DATE	MAY 27	MAY 28	JUNE 2	JUNE 6	JUNE 13	JUNE 21	JUNE 28
R.B.C.	4,620,000		5,050,000				5,360,000
Hgb. (Gm.)	11.6		10.5				10.8
W.B.C.	17,600	22,600	28,800	24,800	17,100	11,100	13,500
Neut. (%)	58	67	15	6	9	32	27
Seg. (%)	54	60	10	4	5	27	26
Stab. (%)	4	7	5	2	3	3	1
Juv. (%)					1	2	
Eosin. (%)	11	11	74	69	64	31	29
Baso. (%)	1	1					1
Mono. (%)				2			1
Lym. (%)	30	21	11	23	27	37	42

CLINICAL COURSE

On the second hospital day, the highest temperature was 103° F.; on the third day it did not exceed 101° F. Thereafter it fluctuated between 98 and 100° F., except for an occasional rise to slightly above 100° F.

On the second hospital day, the highest temperature was 103° F.; on the pubic region, where there were irregular, confluent, dull red areas of variable size, some approaching 1½ inches in diameter. At a glance these areas had a resemblance to erysipelas, but there were no raised indurated borders. No new lesions appeared, and on the fourth hospital day the skin was clear except for the lesions over the abdomen and dorsum of the feet, which had assumed a bluish-yellow appearance. On June 3 (eighth hospital day), the skin was normal and the child appeared to be well; however, x-ray evidence of improvement of the pulmonary infiltration was not evident until June 27, at which time there was an eosinophilia of 29 per cent.

From May 27 until June 3, therapy consisted of 20,000 units of aqueous penicillin given intramuscularly every three hours, sulfamerazine in an initial dose of 0.5 Gm. with 0.25 Gm. every six hours thereafter, and 4 c.c. of elixir of Benadryl four times daily.

COMMENTS

This case was very interesting to us because of the rash associated with Loeffler's syndrome; we had no knowledge of such a phenomenon being considered a manifestation of this syndrome. A search of the available literature failed to reveal any mention of a rash of this type until the report of Hoffman and Huard[4] in the July, 1949, issue of *The Military Surgeon*. The rash in their case was first seen as erythematous macular lesions that became maculopapular.

As Loeffler's syndrome is apparently allergic in nature, and since urticarial lesions were seen in our case, we think it logical to assume that the rash was part of the allergic response to whatever allergen was responsible. The report of Hoffman and Huard lend support to this belief.

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PRIMARY HEPATOMA IN INFANCY

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THIS is a case report of a primary liver tumor appearing in infancy. It is the first case of primary hepatoma accepted by the Tumor Registry of the American Academy of Pediatrics. The pathologic findings are significant.

B. M., a 20-month-old girl, was admitted to the Methodist Hospital on April 21, 1948. One month previous to her admission, her mother noted an increase in the size of the child's abdomen but felt this was due to constipation. There was a history of constipation at irregular intervals since birth. No symptoms referable to the genitourinary or respiratory tract were elicited. There was no history of weight loss; to the contrary, the baby had gained 2 pounds in the past month. The developmental history was normal. The father and mother were living and well. There were six siblings in good health, and two siblings were dead from undetermined causes.

Examination of the child revealed nothing unusual, except for the abdomen. A large tumor occupied most of the right side and extended over the midline to the left side of the abdomen. It measured approximately 20 × 15 cm., and had a "pebbly" feel to palpation. The mass was movable and was 3 cm. below the costal margin. The normal liver edge could be felt; it was confluent with the mass and was soft in consistency.

A study by the Genito-Urinary Department noted no involvement of the right or left kidney, pelvis, ureter, or bladder. The lack of any distortion of the renal pelvis or apparent growth above the right kidney, with no displacement of the ureter, definitely ruled out retroperitoneal origin of this tumor.

Further examination by a scout abdominal film, showed the colon and duodenum to be displaced to the left beyond the midline of the abdomen. There were no gaseous shadows whatever within the intra-abdominal cavity on the right side. There was a large mass that seemed confluent with the liver and, in fact, encroached upon the right diaphragm and elevated it to a higher than normal position. The left diaphragm was also elevated.

The preoperative diagnosis of a primary tumor of the liver, such as an adenocarcinoma or a hamartoma, was considered.

The operation was carried out through a long right rectus incision. A large tumor mass confluent with the right lobe of the liver, and apparently covered with Glisson's capsule, was found. It measured approximately 18 × 14 cm. It was soft and spongy in character, and its surface was coursed by many large and small blood vessels. It was freely movable anteriorly, laterally, and inferiorly. Palpation of the right and left kidney, and along the lumbar gutters, did not reveal any tumor mass arising from these sites. In view of these findings, a diagnosis of primary liver tumor was considered and resection of the tumor was attempted. The bleeding encountered became so profuse that it was impossible to control the hemorrhage by clamping, ligation, and Oxycel gauze, and the operation had to be discontinued after approximately three-quarters of the tumor had been resected. The abdomen was closed rapidly in layers, but the patient continued to bleed intra-abdominally and succumbed shortly after the completion of the operation. A post-mortem examination was not permitted.

From the Methodist Hospital, Brooklyn.

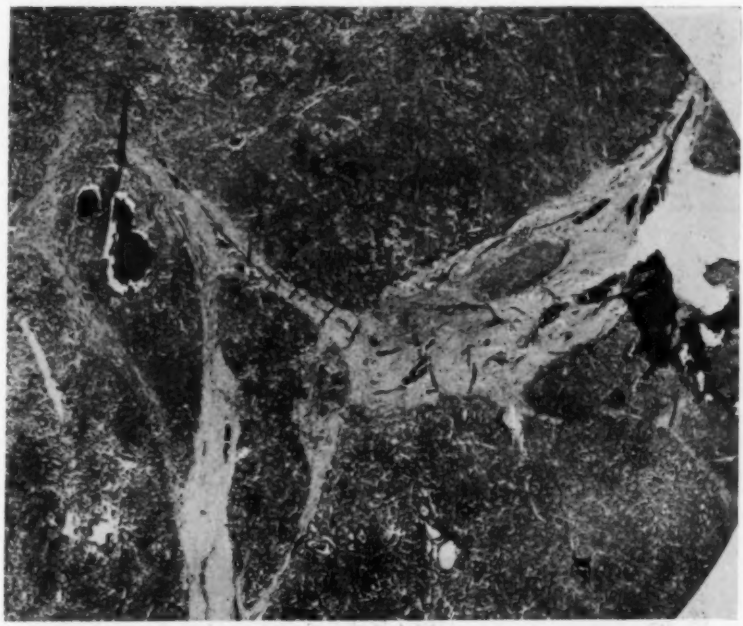

Fig. 1.—Microphotograph showing atypical line cells arranged in cords forming nodules, separated by dense bands of fibrous connective tissue. (×15.)

Fig. 2.—Microphotograph showing areas of hemorrhage and necrosis in tumor. (×15.)

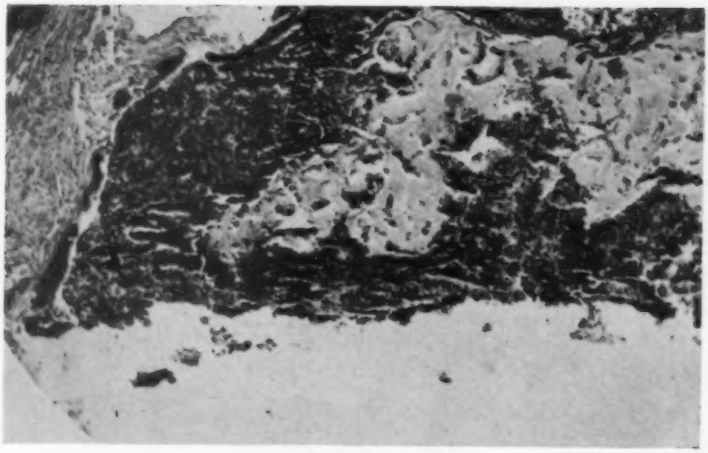

Fig. 3.—Microphotograph of area showing dense hyaline collagenous stroma in a cylindromatous pattern. (×100.)

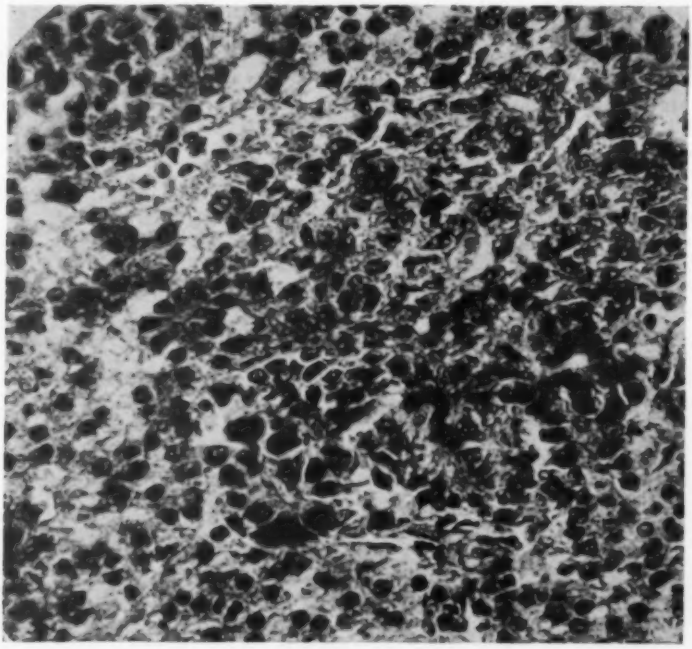

Fig. 4.—High power microphotograph showing cellular detail. (×430.)

The pathologic report by Dr. John S. Howe follows:

A gross examination of the specimen in the laboratory showed a tumor mass measuring 13 × 11 × 9 cm. The surface was irregular, nodular, and the serosa bluish-gray in color. It was rubbery in consistency. A cut-section was yellowish-pink in color, lobulated, and appeared fatty in nature. Calcification was evident by the gritty sensation in cutting.

Microscopic examination showed that sections from various areas of the tumor were similar in appearance. The tumor was composed of masses of large polyhedral cells, some of which closely resembled normal adult liver cells and showed marked vacuolization of their cytoplasm. The cells, however, were arranged in cords and formed irregular nodes rather than lobules showing no normal architecture. These nodules are separated by dense bands of fibrous connective tissue. In some areas the cells were much more anaplastic and atypical in appearance with more hyperchromatic nuclei, occasional mitotic figures, and less marked resemblance to adult liver cells. In a few areas there was a tendency to form acini, but this was not a marked characteristic of the tumor. Scattered throughout the tumor were occasional areas in which there was dense hyaline collagenous stroma in a somewhat cylindromatous pattern, and in some of these areas there was calcific deposition, but no definite bone formation was seen. Several areas of hemorrhage and necrosis of the tumor were noted. There was no definite evidence of invasion of the vessels within the tumor.

REPORT ON A PREMATURE INFANT WEIGHING 822 GRAMS

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WASHINGTON, D. C.

IT IS unusual for premature infants weighing less than 900 grams at birth to survive.[1] In Tyson's[2] series of 384 premature infants weighing less than 2 pounds at birth, only 2 per cent survived. Increased interest in these very small premature infants with attendant improvement in medical and nursing care will serve to decrease the high mortality in this weight group.

Previous reports of premature infants weighing less than 900 grams with survival include those of Fischer-Ban[3] (weight 600 grams), Hoffman[4] (weight 735 grams), and Dale[5] (weight 820 grams). Of the thirty-four premature infants weighing under 1,000 grams at birth, only three survived in the series reported by Taylor and associates.[6]

D. W., a Negro girl, was born Dec. 7, 1946, at Freedmen's Hospital weighing 822 grams (one pound, 13 ounces) after a twenty-four weeks' gestation. The mother was a 28-year-old primipara who admitted overindulgence in coitus during her entire pregnancy. The labor lasted 19½ hours and terminated within 5 minutes of the mother's arrival at the hospital. The infant was delivered by Dr. William B. Russell. The mother had an uneventful post-partum course and was discharged from the hospital three days after admission.

The infant was in fairly good condition at birth. Immediately after birth mucus was aspirated from the throat and the infant was placed in a Maxwell type incubator. Oxygen was administered and the temperature of the incubator was maintained at 90° F. and the humidity at 55 per cent. Vitamin K was given for the first three days of life.

Nothing was given by mouth for the first 12 hours. Initial feedings consisted of 5 per cent glucose water given by medicine dropper every 3 hours in increasing amounts from 2 to 10 c.c. Twenty-four hours after birth, small feedings (5 to 10 c.c.) of Dryco-Dextri-Maltose formula, supplying 28 calories per ounce, were administered.

By December 16, the infant was taking 15 c.c. of formula every 3 hours. This amount was subsequently increased as the infant's tolerance for food improved, to 30 c.c. by December 29, 45 c.c. by January 26, 60 c.c. by February 10, and 90 c.c. by February 21. Oleum Percomorphum (5 drops) was started on the eighth day of life. Ferric and ammonium citrate (a 50 per cent solution) 10 drops daily and vitamin C (ascorbic acid) 25 mg. daily were added. Two whole blood transfusions were given, 10 c.c. on the tenth day of life and 20 c.c. on the seventeenth day of life.

On Jan. 5, 1947, the infant exhibited signs of a mild upper respiratory infection with cyanotic spells. This condition responded within 5 days to ephedrine sulfate nose drops and penicillin administered parenterally.

Spontaneous vomiting and abdominal distension occurred on Feb. 20, 1947. This was relieved promptly when bilateral inguinal herniae were reduced.

From the Department of Pediatrics of Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital.

The weight (see Chart I) remained practically unchanged for the first two weeks. After the fourteenth day of life there was a progressive increase in weight. On Feb. 24, 1947, seventy-eight days after delivery, she was discharged home weighing 2,580 grams (5 pounds, 11 ounces).

The infant was followed at a well-baby clinic where diet was prescribed and immunization given. She sat erect at age 9 months and walked with support at 12 months of age. Umbilical and bilateral inguinal herniae were no longer evident after the sixth month of age. There was no evidence of retrolental fibroplasia.

She was readmitted to Freedmen's Hospital April 5, 1948, at the age of 16 months (Fig. 1) for treatment of acute bronchitis. Her weight was 17 pounds and 12 ounces. Nutrition and tissue turgor were only fair. The anterior fontanel was closed. A hemogram revealed 3.24 million erythrocytes; hematocrit 30 per cent, and hemoglobin 10 Gm. (64 per cent) Sahli. The blood Kahn was negative. A roentgenogram of the hands and wrists revealed a skeletal age of 9 months (Todd Standard).

Fig. 1.—D. W. at the age of 16 months when her weight was 17¾ pounds and the skeletal age (Todd Standard) was approximately 9 months.

The infant was last seen at the age of 19 months when she was brought to the hospital for treatment of acute tonsillitis. She weighed 18 pounds, 9 ounces and was 30 inches tall. She was not talking or walking alone. The circumferences of the head and chest were 17½ and 17 inches, respectively. She had four upper and four lower incisor teeth. Her nutrition and tissue turgor were only fair and the subcutaneous fat was inadequate in amount. Roentgenograms of the upper and lower extremities revealed normal skeletal architecture with no evidence of rickets or scurvy. The bone age was now 12 months (Todd Standard). The hemogram disclosed 3.38 million erythrocytes, 16,000 leucocytes with a normal differential count, hemoglobin 12 Gm. (70 per cent) Sahli, and hematocrit 31 per cent. Except for her small size the child appeared to be normal and mentally alert.

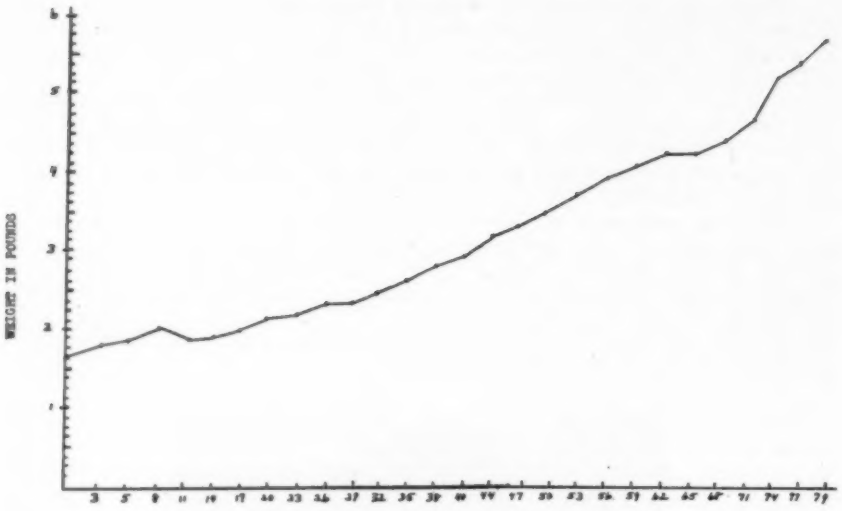

Chart I.—Weight gain. After the fourteenth day of life there was a progressive increase in weight.

SUMMARY

1. A case of survival of a premature infant weighing less than 2 pounds is reported. The infant grew and developed normally as a healthy child.

2. With excellent nursing and medical care more infants weighing less than 1,000 grams can be salvaged.

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Clinical Conference

CONFERENCES AT ST. CHRISTOPHER'S HOSPITAL FOR CHILDREN, PHILADELPHIA, PA.

Case 1. Probable Periarteritis Nodosa (Polyarteritis), With Complications, and Residua of Jacksonian Epilepsy and Personality Changes

CLINICAL SUMMARY

DR. DAVID S. SMITH.—R. W., a 6-year-old Negro boy, was brought to the clinic on Feb. 11, 1949, with a tender cervical swelling associated with fever and an upper-respiratory infection. At this time his tuberculin test and serologic tests for syphilis were negative; his urine was within normal limits except for a trace of acetone, and his white blood count was 13,000 per cubic millimeter with 67 per cent neutrophiles, 29 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophiles. A throat culture revealed hemolytic *Streptococcus viridans*, diphtheroids, *Neisseria sicca*, and *Neisseria flava*. The diagnostic impression was acute cervical adenitis. Therapy included sulfadiazine, 0.6 Gm. every four hours, and the application of heat over the tender node. Recovery appeared to be complete four days later and the therapy was discontinued.

The past medical history revealed that in April, 1947, he was seen in the clinic with giant urticaria. There was no history of colic during infancy or of eczema or hay fever, nor of other respiratory or gastrointestinal allergy. His family history was noncontributory; specifically, there was no history of allergy. The patient had been immunized against diphtheria, pertussis, tetanus (triple vaccine), and smallpox.

On Feb. 19, 1949, he was admitted to the hospital with the complaint of swollen ankles. He was afebrile. There were pin-point to dime-sized purpuric spots over both tibiae, and swelling and erythema over both ankles without perceptible evidence of local heat and without pain on motion. The tip of the spleen was now palpable, and there was a soft, grade I precordial systolic murmur. Two days after admission he developed marked oliguria. His blood pressure was in the range of 110/80. Visible edema of the ankles and face appeared and he gained 2 pounds in weight during the first three hospital days. A small amount of urine obtained on Feb. 22, 1949, showed 5.2 Gm. of albumin per 100 c.c., from 4 to 5 red blood cells, and from 8 to 10 white blood cells per high-power field. Because of the possibility of ureteral blockage resulting from the previous administration of sulfonamides it was felt advisable to catheterize the ureters. A small amount of urine was obtained by this method on Feb. 23, 1949, while under ether anesthesia. The oliguria persisted for three more days, during which time 250 c.c. of 2½ per cent sodium sulfate in addition to other fluids were administered daily by the intravenous method. The blood urea nitrogen rose to 143 mg. per cent. Following diuresis it returned to the normal range. However, the blood carbon dioxide combining power rose to 46.4 meq. per liter and his sodium chloride became depressed to 69.2 meq. per liter. Hydrochloric acid and calcium chloride were then administered. Under this regimen, the

edema decreased, the carbon dioxide dropped to 22.3 meq. per liter, and the sodium chloride rose to 114.6 meq. The blood urea nitrogen remained within normal limits.

By the March 12 there was a marked decrease in the urinary albumin, but the sediment continued to show from 20 to 100 red blood cells and an occasional hyaline and granular cast per high-power field. On this date he complained of abdominal pain and developed marked abdominal distention, an enlarged, tender liver, evidence of a small right pleural effusion, gallop rhythm with an apical rate of 144, and a loud, blowing systolic murmur heard best just lateral to the sternum in the third left intercostal space. His blood pressure at this time was 176/140 and he rapidly lost consciousness. Therapy at this time consisted of magnesium sulfate, oxygen, and digitalis. Twenty-four hours later he began to have twitchings of the right side of his body. His spinal fluid pressure was 410 mm. of water. There was no response to therapy, and his condition remained critical, On March 17 he developed moderate nuchal rigidity. There were no obvious palsies, the deep reflexes were generally hypoactive, and Brudzinski's sign was positive. In addition to a general hypotonia, there was a tendency toward bilateral wrist drop and definite weakness of the right leg and arm. When the spinal fluid was found to be cherry red in color it was attributed to a spontaneous subarachnoid hemorrhage.

He regained consciousness on March 22, but was totally blind. His blood pressure was in the range of 200/140, and his spinal fluid pressures obtained daily were in the range of 450 mm. of water. Attempts to maintain his nutritional status by gavage feedings were unsuccessful and he became extremely malnourished. By March 26 he was able to sit up and had some use of his right arm and hand.

On March 30, he had sudden and extremely severe abdominal pain. Abdominal distention became marked and he repeatedly vomited fecal-stained material. A roentgenogram revealed distended loops of bowel with fluid waves in the small and large intestines. Laparotomy disclosed a large amount of light yellow turbid fluid. Approximately 1,000 c.c. were removed. There were large sheets of plastic exudate covering the small bowel. Palpation of the mesentery revealed a succession of stringlike indurations which were thought to be thrombosed or sclerosed blood vessels. An obviously thrombosed vessel was removed for histologic examination, and an appendectomy was performed. Culture of the peritoneal fluid yielded *Escherichia coli*.

On April 5, edema reappeared on the face, hands, and feet. His speech became rambling, his sensorium confused, and on April 8, he was again in a comatose state. His blood pressure was 212/180, and it was thought that death was near. His urine was free of albumin at this time and contained only a few red blood cells. The specific gravity ranged from 1,002 to 1,021.

On April 18, there was a remarkable degree of improvement and he was able to answer questions. His blood pressure was now only 110/80. On May 1, there was evidence that his vision was returning, and on May 4, he was able to read a comic book.

On May 5, he passed light-colored stools and had a moderate degree of icterus. His liver was not palpable; he was afebrile and eating well. The Van den Bergh reaction was immediate direct, the icterus index was 25, and the cephalin flocculation test negative. His stools became darker by May 10, but were bulky and foul-smelling. The icterus rapidly disappeared. His convalescence from this time was rapid, he became alert and happy, and gained weight. On May 14, 1949, approximately three months after admission, he was discharged from the hospital.

In the next few weeks, during which time he was observed in the Out Patient Department, his progress continued to be favorable. Urinalyses, blood pressure, and eye grounds were all within normal limits. The Stanford-Binet Test revealed a mental age of 6 years and 4 months, with an I. Q. of 94. Although he was an active boy before his illness, overactivity of a disturbing degree was now noted. In June vision was 20/50 in each eye and in September he was able to return to school. Although he seemed to do well scholastically, his antics constantly disrupted the classroom. In October, 1949 he developed a respiratory infection and was seen during a typical asthmatic attack which responded to adrenaline.

On January 6, 1950, while in school he had a convulsion involving the right arm and leg and was again admitted to the hospital. The blood pressure at this time was 160/100, pulse 140, and respirations from 18 to 22; his temperature was normal. The blood urea nitrogen was 8 mg. per cent and the spinal fluid pressure was 140. The convulsion was controlled by sedation and he was alert twenty-four hours later, but showed residual weakness of his right arm and right leg. By Jan. 9, 1950, he required sedation because of his hyperactivity on the ward.

On February 3, he was again admitted to the hospital because of a second convulsion involving principally the right side of the body. Following recovery from the convulsion he again showed the evidence of hyperactivity behavior problems which had been manifest in the period of time since his initial dismissal from the hospital.

The personality changes in this boy seem significant. Prior to the initial hospital admission, he had been a tractable, likeable youngster who had not manifested any unusual behavior problems either at home or in school. Before his discharge from the initial admission to the hospital, he became quite unstable. He had periods when he became quite abusive to nurses, doctors, and the other patients on the ward. Such outbursts were usually followed by periods of contriteness and a recognition of the disturbance that he had caused and a wish to avoid such outbursts in the future. However, the pattern did not change in the hospital, and at home and in school he subsequently became quite unmanageable. For this reason it is planned to have him admitted to an institution where he can be more thoroughly studied and therapy provided for the behavior disturbance.

PATHOLOGIC REPORT

DR. JAMES B. AREY.—Sections of the appendix revealed a heavy exudate of neutrophiles in the serosa. Several arteries in the appendiceal wall were thick-walled and showed fibroblastic intimal proliferation; one small artery was completely occluded by such proliferation, and in the adventitia of this vessel there was an infiltrate of plasma cells and small lymphocytes. Another thick-walled, small artery was surrounded by a heavy collar of small lymphocytes, and a few of these invaded the outer media. The inner portion of the wall of this vessel, which was almost occluded, was replaced by a bright pink zone of fibrinoid necrosis. A few arteries revealed almost complete replacement of their walls by similar zones of fibrinoid necrosis.

Section of the mesenteric vessels showed small perivascular accumulations of plasma cells, lymphocytes, and neutrophiles with a more diffuse infiltrate of these cells beneath the serosal surface. Four medium-sized arteries were completely occluded by organized thrombi. The internal elastic lamella was still demonstrable in some areas as a broad, pink wavy band. In a few areas pyknotic fragments of nuclear material were present in the vessel walls, and in a few areas there was hemorrhage in the vessel wall. Numerous fibroblasts were present in the adventitia of these vessels, often arranged in a palisade-like fashion. About these there were abundant phagocytosed hemosiderin pigment granules, scattered neutrophiles, lymphocytes, and plasma cells. In a number of areas the vessel wall appeared to be largely, if not completely, replaced by necrotic material and fibroblasts. No eosinophilic infiltrates were noted.

The histologic findings were considered compatible with a diagnosis of polyarteritis (periarteritis nodosa), although the possibility that the arterial lesions were secondary to the inflammatory process could not be excluded. In view of the clinical course of the patient and the pathologic findings, the diagnoses were (1) probable polyarteritis (periarteritis nodosa), and (2) peritonitis, probably secondary to thrombosis of the mesenteric arteries.

SYNOPSIS OF DISCUSSION

Initially it was thought that the clinical pattern could be explained on the basis of an acute glomerulonephritis with hypertensive encephalopathy. As the clinical condition became more severe and the wide variety of manifestations made their appearance, it became increasingly doubtful that this was the explanation, or at least the sole one. The possibility of periarteritis nodosa or polyarteritis was considered and the diagnosis was thought to be established by a histologic examination of the mesenteric vessels. Perhaps this diagnosis should have been suspected earlier because of the purpuric skin lesions which were present at the time of admission. However, purpura associated with glomerulonephritis is not unusual and, in itself, is not a differential factor. Whether all of the clinical findings can be explained on the basis of polyarteritis is a question. Certainly it is possible that the kidney findings of albuminuria, hematuria, and oliguria, the hypertension, the encephalopathy, the spontaneous subarachnoid hemorrhage, the hemiplegia, the blindness, the peritonitis apparently secondary to mesenteric thrombosis, the congestive heart failure, and the pleural effusion could all be the result of a widespread polyarteritis.

Whether the symptoms of asthma can also be the result of it is not so certain. Certainly those associated with cardiac failure could be, and possibly even the same antigenic mechanism could have been responsible for a transient bronchospasm. However, the possibility of some other allergen being responsible for this manifestation must be recognized.

The question was raised whether the jaundice which appeared to be obstructive in type might also be a manifestation of the disease. Multiple hepatic infarcts may occur in polyarteritis. In addition, a pylephlebitis secondary to the necrotic lesions in the intestines cannot be excluded as a causative factor. The clinical course of the jaundice and the period of time elapsing between the appearance of jaundice and the peritonitis make this possibility somewhat unlikely. At the time that this boy had jaundice, there was a fairly high incidence of infectious hepatitis in the Outpatient Department and in the hospital, and it was the consensus that an intercurrent infectious hepatitis was the more likely possibility.

If periarteritis nodosa or polyarteritis is responsible for the clinical pattern described here, it is of some interest to note that at no time were subcutaneous nodules demonstrable, that the percentage of eosinophiles in the peripheral blood never exceeded 5 per cent, and that the child was afebrile for the first three weeks of his initial hospital admission.

In the discussion of the possible causes for the arterial changes in this boy, sensitization to a bacterial protein was considered, as was sensitization to a sulfonamide. This latter cause was considered to be the more likely by a number of those present.

At the time of this writing, it would appear that the disease process itself was inactive but that the residua of jacksonian epilepsy (right-sided) and personality changes were the direct result of the polyarteritis. It will be of considerable interest to follow the subsequent course of this boy from the standpoint of these latter two factors as well as for the possibility of subsequent manifestations of the disease itself.

Case 2. Thrombosis of the Renal Vein With Infarction of the Kidney

CLINICAL SUMMARY

DR. DAVID S. SMITH.—D. S., a 3-month-old white male infant, was in his usual state of good health until two weeks prior to admission to a hospital on Dec. 10, 1949, because of vomiting and low-grade fever. At the time of admission marked dehydration was noted. On the third hospital day a routine urinalysis revealed innumerable red blood cells and 3-plus albumin. Subsequently a mass was palpated in the region of the left loin. Roentgenographic findings at that time revealed a filling defect along the left colon, which appeared to be extraperitoneal. An intravenous pyelogram revealed a functioning left kidney and also evidence of a functioning right kidney. The infant continued to have hematuria and on Dec. 20, 1949, was referred to St. Christopher's Hospital for further study to determine, if possible, the nature of the renal disturbance.

Physical examination revealed a well-nourished but extremely pale white male infant. A tender mass was felt in the left loin extending from the costal

margin in the anterior axillary line to the iliac crest and medially to approximately the midclavicular line. This mass was smooth and did not feel cystic or irregular; its general configuration was reniform. The hemoglobin was 6.9 Gm. and the red blood cells 2.57 million. Intravenous pyelography was not diagnostic because of a large amount of gas in the bowel. Cystoscopy and catheterization of the left ureter were done and clear urine dripped from the ureteral catheter. Analysis of this specimen revealed only 2-plus albumin and from 3 to 5 white blood cells per high-power field. Retrograde pyelograms were obtained and were thought to be within normal limits.

After a transfusion of whole blood an exploratory laparotomy was performed shortly after admission and a large bulky mass having the general appearance of a distended kidney was found. The left kidney and adrenal were removed and the infant made an uneventful recovery.

PATHOLOGIC REPORT

DR. JAMES B. AREY.—The kidney was definitely enlarged, being at least 1½ to 2 times the usual size. It was deep purplish-red in color except for one pole, which was pale, yellow, and sharply demarcated from the adjoining hemorrhagic renal parenchyma. The ureter and renal artery revealed no gross abnormalities. The renal vein was distended by a greyish-brown thrombus extending from the line of resection of the renal pedicle into the major tributaries of the renal vein at the hilus of the kidney. The capsule of the kidney was indurated and upon its removal fragments of the underlying renal cortex were torn away. On section of the kidney no demonstrable neoplasm was present. The entire parenchyma, with the exception of the aforementioned pale area at one pole, was dark purplish-red and boggy. The adrenal with one recognizable adrenal vein revealed no gross abnormalities.

Histologic sections of the kidney revealed complete necrosis of the renal parenchyma, only "shadows" of the pre-existing structures being recognizable. The entire parenchyma was packed with red blood cells. The only remaining viable renal tissue was that present in the pale zone at one pole and an occasional thin zone of superficial cortical tissue. Although a considerable infiltrate of small lymphocytes and plasma cells with scattered neutrophiles was present about the periphery of the necrotic material, the inflammatory reaction did not appear to exceed that which might occur as a simple response to noninfected necrotic material. Sections of the renal vein revealed an organizing thrombus completely occluding the lumen and extending into the larger tributaries at the hilus. Sections of the adrenal revealed no abnormalities except for the presence of hyaline thrombi in a number of large veins in the central part of the adrenal. There was an organizing thrombus present in the perirenal fat. Culture of the thrombus in the renal vein was sterile. The diagnoses were thrombosis of the renal vein with hemorrhagic infarction of the kidney and thrombosis of small adrenal and perirenal veins.

SYNOPSIS OF DISCUSSION

In the consideration of the diagnostic possibilities, renal infarction, hydronephrosis, and an embryoma of the kidney were considered the most likely ones.

Initially, renal infarction was mentioned because of the sudden appearance of a mass in the renal area associated with hematuria in an infant who was seriously ill with diarrhea and who had had a severe degree of dehydration. Increase in the infant's temperature while in the first hospital made it necessary to consider a urinary tract infection with a secondary hydronephrosis. This possibility was largely eliminated by the roentgenographic appearance in the retrograde pyelogram and by the persistence of the mass in spite of marked improvement of the infant. Because of the improvement of the infant's condition following the transfusion of blood for a day or two prior to operation, the majority of observers favored the preoperative diagnosis of an embryoma of the kidney.

Thrombosis of the renal vein and hemorrhagic infarction of the kidney should be considered whenever a tender renal mass associated with hematuria, albuminuria, and pus cells in the urine is noted with severe vomiting and diarrhea or other infection. The etiology of the thrombus in the renal vein is unknown, although some authors feel that it results from renal infection. There was no adequate evidence of such infection in the case under discussion. It seems probable that the pathogenesis of such renal vein thromboses is somewhat similar to that of dural sinus thromboses occurring in dehydrated infants, and indeed the two have occasionally been associated with one another. The prognosis is grave and nephrectomy is the suggested therapy.

As in the case of other renal masses, an exploratory operation should not be unduly delayed once adequate function has been demonstrated in the opposite kidney. The differential diagnosis includes embryoma of the kidney, hydronephrosis, solitary cyst of the kidney, and unilateral polycystic kidney. However, a correct preoperative diagnosis is less important than prompt surgical intervention, and this should be carried out without subjecting the patient to a prolonged period of study.

Case 3. Torsion of the Fallopian Tube and Ovary With Infarction of the Ovary

CLINICAL SUMMARY

DR. DAVID SMITH.—G. T., a 7-year-old white female child, patient of Dr. Norman Kendall, was awakened by severe left-lower abdominal pain on Jan. 3, 1950. She described a knifelike radiation of the pain to the genital region. From 8 A.M. to 3 P.M. the pain was continuous, followng which it seemed to become intermittent. Slight pain was also noted on urination. A few hours after the onset of symptoms the patient vomited and continued to do so intermittently for the next eighteen hours. She had had no stool for two days. There had been a similar but much less severe episode about one month previously, and pain in the left-lower quadrant had been noted on three additional occasions, each lasting about two hours. There was no vomiting or urinary complaints during these episodes.

Physical examination twenty-four hours after the onset of the present illness revealed an acutely ill, thin, undernourished female child who lay quietly on her side with her left leg in flexion. She complained of abdominal pain and nausea. Her temperature was 101° F. by rectum, pulse 120, and respirations 18. The abdomen was symmetrical with slight distention. There was general-

ized moderate tenderness with marked tenderness in the left-lower quadrant and a suggestion of a mass near the midline. Peristaltic movements were hypoactive. Rectal examination was unsatisfactory but there appeared to be tenderness in the cul-de-sac. The white blood count was 13,200 with 80 per cent neutrophiles. Multiple examinations of the urine were negative except for the presence of ketone bodies. A flat plate of the abdomen was noncontributory.

After preliminary preparation by the administration of intravenous fluids, an exploratory laparotomy was performed. A small amount of bright red fluid was encountered, and a firm, irregular mass was found in the left pelvic region. This mass proved to be an enlarged left tube and ovary which was twisted 2½ times on its pedicle. The ovary was purplish-black mottled with brown. The appendix and terminal ileum were normal, as were the right tube and ovary. The infarcted mass was excised and the patient made an uneventful recovery.

PATHOLOGY REPORT

DR. JAMES B. AREY.—The speciman consisted of a hemorrhagic, thick-walled Fallopian tube and ovary. The Fallopian tube measured 0.7 cm. in diameter and 5.5 cm. in length. The ovary measured 5 x 3.5 x 3 cm. Its surface was smooth and dark purple, it was boggy to palpation. On section the entire ovary consisted of a hemorrhagic soft mass, of somewhat firmer consistence than might be expected with a simple blood clot. Scattered smooth-walled cystic spaces measuring up to 0.4 cm. in diameter were present within the ovary; grossly these suggested follicular cysts. No neoplasm nor large cyst was demonstrable.

Histologic sections revealed a hemorrhagic mass, the only recognizable structures being scattered necrotic vessels, a rare structure resembling a necrotic follicular cyst, and occasional recognizable ova near the cortical surface. The Fallopian tube was hemorrhagic and necrotic. In none of the sections was there anything suggestive of a solid or cystic neoplasm. The diagnoses were torsion of the left tube and ovary with hemorrhagic infarction.

SYNOPSIS OF DISCUSSION

Although torsion of the pedicle of an ovarian cyst with resultant infarction is well-recognized in adults, it appears to be rare in infants and children. In the present instance, there was no evidence of a pre-existing ovarian cyst, which might by its very weight tend to become rotated on its pedicle with resultant infarction. Here, however, the enlarged ovary and tube can be explained simply on the basis of hemorrhage secondary to venous stasis and infarction, and the etiology of the torsion responsible for this infarction is not explained.

Although in retrospect the intermittent character of the pain and its radiation to the genitals, in the absence of positive urinary findings might suggest the intermittent twisting and untwisting which undoubtedly occurred, the extreme rarity of the condition, plus the absence of a definitely demonstrable ovarian mass would largely preclude a correct preoperative diagnosis. Although such a condition should possibly be considered in the differential diagnosis of lower abdominal pain, its rarity would place it far down in the list of diagnostic possibilities.

Psychologic Aspects of Pediatrics

NAILBITING—A REVIEW

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NAILBITING is a common oral habit in children and young adults.[1-5] Over 80 per cent of a group of World War II inductees were actual or former nailbiters.[3]

Nailbiting may become a problem when it is so vigorous and persistent that it results in the complete destruction of the free margin of the fingernail, leaving tags of soft tissue which suffer from repeated attacks of paronychia.[4] The physical effects, however, are not as damaging as the emotional conflicts from which the habit may arise and to which it may lead. Nailbiting is a sign of internal tension. In addition, whatever the cause, it may lead to emotional conflicts since it is not socially acceptable to parents, teachers, and other persons in authority. Unless the cause, pattern, frequency, and course of nailbiting are analyzed, it is difficult to differentiate between "normal" and "abnormal" nailbiting and the normality or abnormality of the nailbiter. This review is designed to bring together the present findings and interpretations of nailbiting into some logical sequence which would further a better understanding of the act in relation to the total physical growth and emotional development of the child.

Pattern of Nailbiting.—According to Billig,[2] nailbiting follows a sequence of four distinct postures: (1) Placing of either hand in the vicinity of the mouth. This posture continues from a few seconds to half a minute. (2) Rapidly tapping the finger against the anterior teeth. (3) A sequence of quick, spasmodic bitings with the nail of the finger pressed tightly against the incisal edge of the anterior teeth. (4) Removal of finger from the oral cavity. The finger is inspected visually or palpated.

During the entire sequence, the facial expression is rather serious. If the biter becomes aware of being observed, the activity is brought to a sudden end with what is apparently a sense of guilt. Severe nailbiters often find it difficult to discontinue the act even when ridiculed. As a consequence, they find themselves pushed more deeply into conflict with society.

Incidence.—Nailbiting does not occur in children under 3 years of age.[1, 6, 7] Wechsler[1] found that the incidence increased markedly and suddenly between the ages of 3 to 6 years, after which it remained at a fairly constant level (circa 33 per cent) until puberty. The percentage then rose rather sharply to a peak at 13 years of age (43.6 per cent of boys and 44.4 per cent of girls).

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After the grade school level (15 years), nailbiting decreases progressively. Wechsler[1] showed that the incidence quickly drops from 44 per cent at 13 years to about 19 per cent at 16 years. Billig,[2] in a study of high school sophomores (ages 15 to 17 years), on three occasions found the incidence of the act to be 20 per cent, 25 per cent, and 29.4 per cent. Approximately *one-half or more of the nailbiters had desisted by their fifteenth year of life* Undoubtedly, social disapproval (especially by members of the opposite sex), at an age which is becoming sex conscious, forces the nailbiter to transfer to a less obvious mannerism.

The most complete studies of nailbiting in children were carried out by Wechsler[1] in 1931 and Billig[2] in 1941. Confirmatory findings have been added by other authors.[4, 6, 7, 8] However, the criteria of assessment are not standardized, hence the figures presented from different studies tend to vary.

The incidence of nailbiting decreases significantly after the age of 18 years.[9, 10, 11, 12] Pennington[10] examined 6,946 white naval inductees and volunteers. He found that at 17 and 18 years of age one male subject out of 4 revealed the mannerism; at 30 years, the ratio was one in 9; at 37 years, the incidence was one in 12. The prevalence in women is undoubtedly much lower.

From these studies it must be assumed *by reason of its wide prevalence* that nailbiting is "normal" in children from 4 years of age until adolescence, in the sense that "normal" indicates averageness or the commonplace. On the other hand, the low prevalence rate after 18 years of age may indicate that nailbiting, except the very mildest kind, should be considered "abnormal." Certainly after the age of 30, nailbiting should be considered more seriously than merely as a habit. Persistent nailbiting, like persistent thumb-sucking, may indicate emotional and social immaturity or regression.[13, 14]

Sex Differences.—Some authors[5, 15] have found a significant difference in nailbiting between boys and girls. Others [2, 11, 16, 17] claim that no difference exists except that boys tend to *persist* in the habit longer than do girls.

Familial Tendencies.—Some writers have indicated that there is a familial tendency in nailbiting, probably on the basis of imitation.[2, 5, 10, 18, 19]

Intelligence.—All investigators who have related intelligence to nailbiting agree that no correlation exists between the two factors.[2, 5, 15]

Origin of Nailbiting.—It has been suggested that nailbiting is a transfer from the thumb-sucking habit on the basis that thumb-sucking tends to disappear during the third year of life while nailbiting begins at that age.[1, 13, 18, 20] This chronological relationship is supported by clinical appraisal and longitudinal study of children from 2 to 5 years of age.[1, 13, 18, 20, 21]

Many writers have postulated a psychosexual basis for oral habits. This viewpoint is based upon Freud's[22] stages in psychosexual development. Wechsler[1] stresses the fact that finger-sucking is a complement to nipple-sucking and necessary to the infant in order to achieve full oral erotic gratification. Nailbiting is a continuation of the thumb-sucking habit during the genital erotic phase of psychosexual development of the child and consequently has phallic symbolism. The act of nailbiting, like that of thumb-sucking, is therefore an

unconscious (and perfectly normal) form of masturbatory activity. However, nailbiting in contrast to thumb-sucking, carries with it a certain amount of "punishment"—self-punishment in the case of a guilt complex or anger at the parent. For further details of this thesis, the reader is referred to English and Pearson[14] and to Menninger.[23, 24]

Not all writers accept this point of view.[2, 5, 10, 25, 26] Most authors agree that finger-sucking serves a definite need for oral gratification in the infant and agree also that nailbiting serves to satisfy a similar need in the older child. They do not feel, however, that it is necessary to invoke a phallic symbolism or genital connotation to the mannerism—that such an explanation is "more concealing than revealing."[10]

Substitution for Nailbiting.—Nailbiting originates as a transfer from thumb-sucking some time between 4 and 6 years of age when social (parental) censure demands that sucking habits be discontinued. In turn, nailbiting must be discontinued when society again demands it. Most children successfully resist parental demands to stop nailbiting, but sometime after the age of 15 years the censure of friends makes it expedient for the average gregarious child to substitute some other "habit." These substitutions range from the relatively innocuous pencil-biting and gumchewing to the more surreptitious lip-biting, nail-picking and nose-picking.[18, 27] Gumchewing offers a socially acceptable method of oral gratification. In fact, it is a good method of "transferring" habitual nailbiting.

In the adult, smoking is a common nailbiting substitute. The cigar sometimes replaces the finger in the adult's need for oral gratification. The compulsive chain-smoker frequently gives a history of severe nailbiting in childhood. Hair-twirling, nose-picking, and even "doodling" are considered as "transfer habits." Billig[27] regards such tranfers as "equivalent mannerisms" which are a reflection of the personality of the child.

Persistent Nailbiting.—Nailbiting usually ceases during adolescence. However, it may become fixed and persist long after that time if too much ridicule is heaped upon the nailbiter by parents, teachers, or playmates. Similarly, a mild nailbiting habit during childhood may become very severe if too much attention is given to it by parents. In this respect, the emotional constitution of the child plays a great role since it determines the character of the reactions of the child toward the condemnations heaped upon him.

Effects on the Dentition.—Nailbiting is mentioned in the orthodontic literature as a causative factor in the malpositioning of the anterior teeth.[28, 29, 30] These references are vague and always considered under generalizations such as "habits." We could discover no objective evidence, clinical or statistical, to prove that nailbiting causes dental malocclusion. Schwartzman[4] quoted other authors as having noted dental trauma, gingivitis, and herpes resulting from nailbiting. However, this seems to rest more on opinion of what should happen rather than upon direct observations of what did occur.

Only one case was discovered in the literature[31] in which *vigorous and continuous nailbiting* caused alveolar destruction about the teeth used in biting.

Lack of evidence in the literature as well as personal observations indicate that ordinary nailbiting has no serious effect upon the dentition. This is probably because it does not differ from common biting and incising during mastication. In contrast, sucking habits (thumb-sucking, lip-sucking, and tongue-sucking) frequently do cause malocclusion, especially during the critical, mixed dentitional period, 6 to 12 years of age. Sucking involves the use of the labial and lingual musculature in an abnormal fashion, upsetting the delicate muscular balance which molds the developing arch during the mixed dentitional period. Nailbiting, on the other hand, does not involve the abnormal use of oral muscular forces.

Nailbiting in Situations of Stress.—Most persons bite their nails in moments of stress. Children bite their nails in moments of anguish, i.e., when they fear not knowing a lesson, read sad stories, listen to radio horror stories, or are "forced" to go to bed at night.[32] Jones[33] found that school children show increased nervous movements under the stress of working arithmetic problems.

Children who feel rejected seek solace in their fingers.[32] Viets[15] pointed out that nailbiting is often a *reaction* to a deep emotional strain and is greatly aggravated by unhappy environmental conditions (such as those found in broken homes, homes where harmony was lacking and quarrelling was constant, or homes in which there was an alcoholic or immoral parent). Overprotection and sibling jealousy were also found to influence the production of nailbiters.

Goldfarb[34] noted that more than twice as many children reared in institutions had "habits" of nailbiting, nose-picking, or lip-sucking as compared to those reared in foster homes. This was most evident in the 8½-year-old child. Goldfarb implied that the institutional environment created more internal tensions than did the foster homes.

During the recent war, studies were made on the effects of environmental stresses and emotional strains upon the behavior patterns of men during and after combat.[12, 35] Hill[12] found that nailbiting occurred most frequently when the men were in tense emotional situations or during periods of enforced inactivity. All authors agree that nailbiting increases in prevalence and in degree under situations of emotional tension.[10, 12, 35] The adage that persons under tension "bite their nails" seems to be true.

Nailbiting in Abnormal Children.—Especially severe and persistent nailbiting has sometimes been considered a "neuropathic trait" rather than a "habit." A sizable literature has accumulated concerning the occurrence of this mannerism in abnormal personality types.

Delinquents.—Michaels[36] found that 11.7 per cent of 105 delinquent children and 6.7 per cent of nondelinquent children were nailbiters. However, this is not a statistically significant difference. Shahoviteh[8] stated that the majority of juvenile delinquents were nailbiters. She did not present data to support this thesis.

Enuretics.—Anderson[37] found nailbiting in 68 per cent of enuretic girls and 41 per cent of enuretic boys. He concluded that nailbiting appears to be an outlet for emotional tensions arising from the conflicts incident to enuresis.

Michaels and Goodman[38] studied a group of 475 enuretic children aged 6 to 19 years in an attempt to correlate enuresis with other "neuropathic traits" such as temper tantrums, stuttering, nailbiting, etc. Fifty-one per cent of these children were nailbiters. However, nailbiting was not found to enter significantly in the statistical association with enuresis. Nevertheless the authors concluded that there is a "natural" clinical correlation of these "neuropathic traits" with enuresis, which indicates a symptom complex rather than causal relationship among these traits.

Viets[15] found that although a slightly greater number of enuretics were found among nailbiters than among non-nailbiters, the difference was not significant.

Stutterers.—Oral habits were found to be common in a group of fifty stutterers, aged 6½ to 15 years.[21] Thumb- and finger-sucking, common at an early age, were replaced in later years by nailbiting. Despert[21] stated that nailbiting in this group was a sign of general tensions and principally an index of oral tension. About half of the group showed severe nailbiting, and nearly all were observed to bite the nails habitually.

Nailbiting in Abnormal Adults.—The studies of psychoneurotic rejectees and evacuees during World War II[12, 39] and the findings in schizophrenics and adult enuretics[40, 41] showed clearly that nailbiting occurred with greater frequency in abnormal personality types and adults with unresolved fears and problems than in so-called normal persons.

Summary.—It is clear that nailbiting itself is not indicative of any abnormality in personality. None of the investigators is willing to consider nailbiting *per se* as a "neuropathic trait," nor is there any real evidence in favor of that view. All investigators agree, however, that it is a significant mannerism when considered with *other* "neuropathic traits" (such as enuresis and stuttering) in the evaluation of the total personality.[39, 40, 41]

It must be pointed out that, even in these rather critical studies, the *degree* of nailbiting observed was not clearly stated nor consistently considered. It seems illogical to include both the mild, occasional nailbiter and the severe, persistent nailbiter in the same group. Certainly from a clinical point of view the "habitual" nailbiter should be evaluated more critically than the occasional nailbiter.

Significance of Nailbiting.—Although the wide prevalence of nailbiting in grade-school children attests to its averageness or "normality," it should not be implied that it is insignificant and unworthy of attention. Nailbiting is evidence of internal tensions. In most cases, these are the ordinary, unavoidable tensions of the average home and school environments. Nonetheless, their existence should be recognized and, if possible, evaluated.

The severe, persistent nailbiter should be scrutinized carefully since the very nature of the act must be significant and indicative of more than ordinary internal tensions. Even a mild or "normal" degree of nailbiting merits at-

tention by the pediatrician and the pedodontist who are attempting to more completely evaluate the total personality of the child. The fact that nailbiting is "normal" does not necessarily imply that it is "ideal" nor even desirable.

All children are subjected to a bombardment of "must's" and "must not's" and live in an environment of frequent frustrations which inevitably create tensions. When these frustrations and tensions are mild and the child is an adaptable one, a "normal" situation results. If the tensions are severe and the child is not very adaptable, neurotic tendencies begin to appear. Enuresis, severe nailbiting, and similar manifestations, are signs of the unresolved conflicts. If nailbiting is evaluated within the total picture of the child's personality, it may become a significant behavior characteristic.

Nailbiting, like any habitual act or "oral habit," must therefore be carefully evaluated since it may be normal or abnormal, desirable or undesirable, depending upon the conditions under which it occurs: (1) the age of the nailbiter, (2) intensity and frequency of the action, (3) relation to the situation in which it occurs, and (4) the emotional status of the biter.

All these factors must be considered lest we fall into the "bad habit" of cataloguing all nailbiting as a "bad habit." The significance of the act depends upon the interplay among all these factors. It may be normal in the grade-school child, if mild and occasional. In the older child, it may be a symptom of regression, especially when it is frequent and intense. When the act is persistent and very severe, it may be part of a neurotic syndrome. Clinically, then, these are all-important considerations which condition one's interpretation of whether nailbiting is "normal" in a particular patient.

MANAGEMENT

Mild Nailbiting.—In cases of mild nailbiting "treatment" is usually not indicated. The child will probably transfer to some other activity at a later age. Parents and friends should not direct attention to this behavior by scolding, nagging, or ridicule. The danger lies not in the act itself but in its condemnation by the parent with the result that it may become fixed. If too much attention is paid to the nailbiting, the child may subconsciously utilize this habit to focus attention upon himself. In other words, overemphasis on the habit merely serves to fix rather than to dissipate it.[42, 43]

Severe Nailbiting.—This may indicate strong internal stresses. Treatment here should be directed toward seeking and *removing the basic emotional factors causing the act.* One should not treat the nailbiting, but the cause of the biting. A child will bite his nails excessively under conditions of excitement, overstimulation, or unhappiness.

In most cases, the only treatment necessary is a little more affection, sympathy, and understanding, with fewer demands by the parents. The child should be encouraged to pursue vigorous muscular activity outdoors, such as skating, running, or ball playing. These activities serve to release the pent-up energy which otherwise would be expressed as tension, leading to nailbiting.

Punitive Methods versus "Reminding" Methods of Treatment.—Harm may result from an unintelligent view of the act. Punishment (physical or verbal)

may lead the nailbiter to social conflict and feelings of guilt. In most instances, therefore, education of the parents is the best "treatment" of nailbiting.

All punitive measures, intentional or otherwise, are to be condemned. The application of bitter substances or restraints to the finger as a punitive measure is condemned by those who are well-versed in the emotional aspects of child development. Louttit[44] stated that such procedures are. . . "even more harmful and contraindicated for nailbiting than for thumb-sucking. Therapeutic measures must be aimed at relieving the underlying tensions, and this involves treatment of the child's whole personality."

Isaacs[45, 46] discredited negative methods:

"I have accumulated . . . evidence showing the uselessness of negative methods . . . whether these take the form of scolding, whippings, tying the hands . . . or putting bitter aloes on the nails. These methods invariably fail . . . cause misery and guilt in the child. . . . I have had several cases in which nailbiting has been cured by the treatment of the nail with olive oil. The physical effects of olive oil on the nails is an important factor. The oil makes the nails smooth and soft . . . no jagged edges . . . the child has less temptation to tear at them. . . ."

A sympathetic approach to the child and a desire to help will usually win his cooperation, since he does not want to bite his nails any more than society wants to watch him bite his nails. Once willingness and cooperation are won, measures to "remind" the nailbiter are generally effective. One can use nail polish in the female; an "expensive" manicure (by a beautician, not by the parent), is surprisingly effective. A simple bandage to cover the "wounded" fingers is very effective once the boy (and his friends) are made to understand that this is treatment for the injury and not for the nailbiting.

SUMMARY AND CONCLUSIONS

1. Nailbiting is one of the most common habits observed in children and young adults. It begins between the ages of 3 and 12 years. The incidence rises sharply from 4 to 6 years of age, remains level between 7 and 10 years, and rises again to a peak during puberty. The incidence among some school children exceeds 40 per cent. Nailbiting decreases markedly during adolescence and is unusual during adulthood.

2. Nailbiting is "normal" between the ages of 4 to 18 years as indicated by the high prevalence during these years. Simple, occasional nailbiting merits little attention other than the fact that it is evidence of some degree of internal tension. However, severe, persistent nailbiting may be a significant symptom. There is a real need for a clear objective definition and distinction between mild and severe nailbiting so that future studies might more exactly coordinate their data.

3. Nailbiting, as a rule, stems from a condemned thumb-sucking habit. The act may become fixated and aggravated by parental condemnation. It may also be intensified by environmental stresses and strains as well as emotional insecurity. Usually, however, it is replaced sometime during or after adolescence by some other socially more acceptable oral habit such as lip-biting, gum-chewing, or smoking.

4. Nailbiting is a simple tension-reducing mechanism, particularly under conditions of situational stress. There is no evidence that simple, mild nailbiting is a "neuropathic trait" nor can the habit be considered as indicative of pathologic personality. It is unrelated to sex or level of intelligence.

5. Nailbiting is frequently implicated in the orthodontic literature as a causative factor in the malpositioning of the anterior teeth. No proof has been discovered to support this hypothesis.

6. Punitive methods in the "treatment" of nailbiting (bitter substances, restraints, scolding, nagging, and threats) are valueless and, in fact, undesirable and even detrimental. Since nailbiting is symptomatic in nature, "treatment" should be designed to reduce environmental stress, increase the feelings of adequacy and security, and thereby relieve the inner tensions.

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Comments on Current Literature

THE EFFECT OF ANTIBIOTICS ON THE VIRUS OF PRIMARY ATYPICAL PNEUMONIA: LABORATORY STUDIES

CLINICAL studies concerned with the use of aureomycin in the treatment of primary atypical pneumonia in human subjects have indicated that this antibiotic is effective in shortening the course of the disease. Unfortunately, however, comparatively few of the published reports are sufficiently complete to exclude entirely other etiological agents, such as those of influenza, psittacosis, ornithosis, and Q-fever, which in man may produce manifestations indistinguishable from the ones associated with the disease entity referred to by clinicians as primary atypical pneumonia. The fact that aureomycin seems to be effective against several of these etiological agents has confused the situation further.

In the January issue of the *Proceedings of the Society for Experimental Biology and Medicine,* Eaton[1] reports carefully controlled laboratory experiments which give support to the somewhat empirical clinical conclusion that aureomycin is effective in the treatment of primary atypical pneumonia. Such studies may also serve to elucidate the nature of the etiological agent.

As early as 1942, Eaton, Meiklejohn, and van Herick[2, 3] isolated a virus from the sputum and from the lungs of patients with clinical findings suggestive of primary atypical pneumonia. They succeeded in infecting chick embryos and in transmitting the infectious agent to cotton rats and hamsters. Immunologic studies carried out on patients with pneumonitis of this type revealed increasing titer of humoral antibody to the newly isolated virus in 60 per cent of the patients tested.

Using well-established strains of this virus, passed twenty-six to thirty times in eggs, Eaton attempted to demonstrate objectively and under carefully controlled conditions, the effect of aureomycin and of Chloromycetin on the etiological agent of primary atypical pneumonia. Cotton rats and fertile hens' eggs were used in the investigations. The cotton rats were inoculated intranasally with a 20 per cent suspension of chick embryo known to contain an infective titer of virus. The antibiotic was administered once daily by the intraperitoneal route, and administration was begun twenty-four hours or more following the inoculation of virus. The experiments were terminated ten days after the inoculation of virus, at which time the extent of the pulmonary lesions was established and recorded.

Studies using aureomycin as the antibiotic indicated that this substance was effective in the treatment of the viral infection in cotton rats when administered in dosages ranging from 20 to 100 mg. per kilogram of body weight, from twenty-four to ninety-six hours after inoculation with virus. When treatment was

delayed longer than ninety-six hours following virus inoculation, the antibiotic was less effective. Comparable experiments with aureomycin were carried out in infected chick embryos, and the results obtained showed that aureomycin brought about a considerable reduction in the amount of active virus present in the chick embryos.

Preliminary investigations of a similar nature in which Chloromycetin was substituted for aureomycin in the treatment of cotton rats inoculated with the virus of primary atypical pneumonia, showed that Chloromycetin in doses up to 400 mg. per kilogram of body weight was of questionable value.

The experimental work reported by Eaton indicates that aureomycin exerts a definite inhibitory effect on the virus of atypical pneumonia. The dose needed for the control of the infection in cotton rats varied from 20 to 100 mg. per kilogram of body weight, depending on the lapse of time between the infection and the initiation of treatment. Such results in experimental animals are in good agreement with the published reports concerning the use of aureomycin in treatment of atypical virus pneumonia in man. It is of considerable interest that filtration data indicate that the virus of primary atypical pneumonia may belong to a group of viruses somewhat smaller than the psittacosis-lymphogranuloma group which is also inhibited by aureomycin. The unsatisfactory results obtained with Chloromycetin suggest that aureomycin is the drug of choice in the treatment of primary atypical pneumonia.

The report of this work is of special interest to the practitioner in that experimental evidence now lends support to the clinical observation that aureomycin is a useful therapeutic agent in the treatment of primary atypical pneumonia.

RUSSELL J. BLATTNER.

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News and Notes

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Dr. John W. Parrish of Brooklyn, N. Y., died Nov. 24, 1949.
Dr. Lendon Howard Smith of Portland, Ore., died Dec. 21, 1949.

The **International Union Against the Venereal Diseases** will hold its twenty-seventh assembly in Zurich, Switzerland, immediately following the International Congress of Pediatrics. A joint session of the members of the Pediatric Congress and the International Union Against the Venereal Diseases will be held on Friday, July 28, 1950.

At the close of 1949, the **Public Health Service** reports that 35 new institutions were in operation under the Hill-Burton Act and 355 were being built. Some 1,300 research projects were being aided in over 200 institutions such as universities and hospitals. Aid has been given to 437 research fellows. Appropriation and contractural authorization for the fiscal year 1949 for the Public Health Service totalled 237 million dollars. Sixty per cent of this was for grants-in-aid to states and communities for general public health activities and hospital construction, and to institutions and individuals for research.

Book Reviews

Problems of Infancy and Childhood. Transactions of the Third Conference, New York, 1949, Josiah Macy, Jr., Foundation, 156 pages.

This is a volume containing the discussion at the Third Conference held in New York, in March, 1949, and is edited by Dr. Milton J. E. Senn. Like the previous discussion, the attendance was limited to a group of twenty-five pediatricians and psychiatrists. The chief themes for discussion were the anxieties of mothers as verbalized to physicians, the psychologic situation of the mother with her newborn child on returning home from the hospital, and the emotional reactions of children to tonsillectomy. There is much of interest in the themes and discussion. The conference is kept small so that all present may participate in the discussion in an informal way. While this undoubtedly added to the value and spirit of the conference for those who attended, the presentation of the conference in print in this way seriously detracts from its general value. Much of the discussion sounds trivial and unimportant and strays far from the theme in a way that is difficult for the reader to follow. Had he been present, perhaps the connection would have been clear, but it is certainly not apparent in the transactions. The reader gets the impression that some of the discussants present just had to say something whether or not it added to the discussion. The themes are all of interest, and had the discussions been summarized rather than personalized and the text cut to about one-third, it would have made an interesting report reflecting some of the present-day thinking along these lines.

If You Have a Deaf Child. A Collection of Helpful Hints to Mothers of Deaf Children. Urbana, 1949, University of Illinois Press, 134 pages. (Copies may be obtained from the Division of Services for Crippled Children, 1105 South Sixth St., Springfield, Ill.)

This is an excellent, well-printed pamphlet which grew out of an annual institute for mothers of deaf children started in 1945. A number of experts in the field have cooperated in discussing their problems with particular emphasis on training of the children. It should be of great aid in helping mothers understand the methods of training and the problems of growth and development and the emotional problems that must be faced with a deaf child.

Children with Mental and Physical Handicaps. J. E. Wallace Wallin, Ph.D., New York, 1949, Prentice-Hall, Inc., 525 pages. Price $6.65.

The author is a psychologist with forty years' experience in the care and education of handicapped children, who has done extensive research and reading in this subject. His book is intended to serve as an up-to-date reference for all professional workers in this field: educators, psychologists, social workers, pediatricians, and psychiatrists; as well as for "the intelligent layman."

The material presented is drawn more from reading than from personal experience. What the author really presents is a rather scholarly review of the literature on mental deficiency, the nature of mental defect, its various classifications, etiologies, and clinical types. The review is critical, but in a conservative way. Only the more important studies receive a real evaluation; most of the time the author is content with merely reporting what has been said or done. The bibliography, on the other hand, is immense and easy to use. The bibliography itself is of considerable value.

The writer's approach is more scholarly and philosophical than practical or investigative. The interested pediatrician will not find sections on the clinical handling of mentally handicapped children, their education, or the social problem which they create. The first half of the book deals with theories of mental defectiveness, definitions, and classifications. The second half contains descriptions of the various organic conditions which can produce mental deficiency. Although the author is not a physician, he does not confine himself to the psychologic aspects of these conditions. The book is written for a large lay, as well as a medical, audience, and there is a good deal of space taken up by explanations and digressions on medical subjects that would be superfluous in a book written purely for specialists.

The book certainly serves its purpose as a reference work. It is not particularly directed at the pediatrician, however, and perhaps should be recommended only to those with special interest in the field of handicapped children.

BAKWIN

Mobilization of the Human Body. Harvey E. Billig, Jr., M.D., F.A.C.S., and Evelyn Loewendahl, M.A., Ph.D., Stanford, 1949, Stanford University Press, 65 pages. Price $2.00.

This well-illustrated treatise has as its thesis the importance of stretching contractured or shortened muscular and fibrous structures as a part of treatment of poor posture as well as a part of the treatment of recovery from rigidity following back injuries, surgery, immobilization from trauma, plaster casts, or other causes, etc. In addition to a consideration of correction of immobility, the authors discuss the relationships between coordination mechanisms and mobility and also briefly outline basic neuromuscular mechanisms.

Of great practical importance is Dr. Billig's belief that carrying out of these mobilizing exercises can act as prophylaxis for low back pain, the pain of dysmenorrhea, and several other somewhat unrelated conditions. Emphasis is on stretching of tightened heel cords, hamstrings, lumbar fascia, anterior hip joint ligaments, and other spine mechanisms. Simple exercises are illustrated which are effective in stretching the shortened structures. Some are home type, others require a therapist.

The reviewer has put some of these principles into practice (particularly the dysmenorrhea exercises for student nurses) but is as yet unable to make a statement about their effectiveness. It would appear that, save following diseases like poliomyelitis, the concept of physical fitness as including wide mobility as well as good coordination and muscular strength is of less importance in pediatrics than in adult medicine.

SEDGWICK MEAD.

Healthy Babies Are Happy Babies. Josephine H. Kenyon, M.D., and Ruth K. Russell, M.D., Boston, 1949, Little, Brown & Company, 310 pages. Price $2.50.

This is a new revised fourth edition of the text on infant care which was first published in 1934. It remains one of the better texts among scores of books covering the same field.

Editor's Column

TRACHEOTOMY IN BULBAR POLIOMYELITIS

THAT fatalities in poliomyelitis stem almost exclusively from the bulbar and respiratory paralytic forms of the disease is an undisputed fact. But there is no such unanimity of opinion concerning therapeutic efforts aimed at reduction of this mortality. The chief issue centers about the value of tracheotomy. As long ago as 1932, Wilson discussed the merits of tracheotomy in bulbar poliomyelitis and cited the cases of two children for whom an emergency tracheotomy was performed after collapse from choking on aspirated mucus, with dramatic relief of symptoms. Galloway in 1943 reported on three cases in which he had done tracheotomy because of troublesome pharyngeal pooling of secretions. Two of the patients recovered and one died. However, tracheotomy received its greatest impetus from the experience of the Minneapolis group in their 1946 poliomyelitis epidemic. Of the 1,830 patients treated in Minneapolis, 400 were diagnosed as having the bulbar form, and among these, seventy-five tracheotomies were done. Forty-six of this group died and twenty-nine survived. It was felt that seventeen of the twenty-nine lived because of the tracheotomy, and that two other survivors probably lived because of the operation. Eighteen tracheotomies were done on patients of the pediatric service at the University hospital, of whom nine died and nine survived. Seven of these, it was felt, lived because of the tracheotomy.

A more recent report by Galloway and Seifert states that among fifteen bulbar cases treated by tracheotomy in the Evanston Hospital in 1947 and 1948, no fatalities occurred. For the same periods the mortality rate in Illinois outside of Chicago for bulbar poliomyelitis was 38.8 per cent, and in Chicago for 1948 it was 27 per cent. The authors say that six of their patients were desperately ill and would have died without tracheotomy.

On the other hand, Stimson, chief of the poliomyelitis service in Knickerbocker Hospital in New York City, maintains that cases where tracheotomy was indicated have not been encountered. Of the last twenty-three patients with bulbar poliomyelitis on this service, only one was lost, plus an additional one that lived only three or four hours after reaching the hospital. The other twenty-one are still alive. Credit for this low mortality rate is given to the expertness of the staff in caring for patients with bulbar poliomyelitis.

The experience of Galloway and Seifert in having no fatalities among fifteen consecutive tracheotomies over a two-year period has led them to the conclusion that the factor of major consideration in the saving of life in bulbar poliomyelitis is the maintenance of an airway which at all times provides for an adequate gaseous exchange. They believe that respiratory obstruction leading to hypercapnia and hypoxia or anoxia accounts for the unfavorable symptomatology including encephalitis, and that death results from this cause rather than from overwhelming infection of the brain stem. They deem it strange that in all the discussion about respiratory obstruction and anoxia, so little attention has been paid to the narcotic and even lethal effects of carbon dioxide accumulation. They are convinced that tracheotomy offers the best chance for life in the patients seriously ill with bulbar and respiratory paralysis.

The men of the Minneapolis group do not minimize the dangers of anoxia, but in addition they believe that a certain number of fatalities will be inevitable as the result of heavy infection of the respiratory and circulatory bulbar centers. According to their studies, these centers are located in the ventral reticular substance of the medulla oblongata at the level of the inferior olive body, just below the floor of the fourth ventricle. They were able to demonstrate extensive inflammatory necrosis in this area in patients who had died with symptoms of respiratory center and of circulatory center paralysis. Of thirty-six patients classified as belonging to the former group, 69.1 per cent died, and of twelve patients in the latter group, 83.3 per cent died. Some 72 per cent of 183 bulbar patients showed symptoms which were interpreted as being due to encephalitis, but since these symptoms would frequently disappear with adequate oxygen administration, it was concluded that much of the encephalitic picture may have been due to hypoxia. Hence the members of the Minneapolis group, with the largest experience in the country, believe that many but not all patients with bulbar poliomyelitis can be saved with tracheotomy.

Both Galloway and Seifert and the Minneapolis group (Priest and Goltz) list similar indications for resorting to tracheotomy. Stimson, on the other hand, states there are only two—bilateral abductor paralysis of the vocal cords and untrained or inefficient attendants. His contention quite properly poses the issue as to whether tracheotomy is an unnecessary, mutilating operation which may as well be omitted, provided other known methods of therapy are expertly carried out.

Our own experience with thirty-nine cases of bulbar poliomyelitis in children during the 1949 epidemic in Iowa coincides more nearly with that of the Minneapolis physicians than with that of Galloway and Seifert or with that of Stimson. Twenty-eight of the thirty-nine bulbar cases had tenth nerve paralysis. Tracheotomy was done on ten of these, of whom four died. Two of the deaths occurred in children who were in extremis when admitted and lived only a few hours after the emergency tracheotomy. Microscopic examination of the medulla and spinal cord in the four fatal cases showed extensive inflammatory and necrotic changes. Our 1949 mortality rate among our bulbar cases was 10.2 per cent as compared with 39 per cent in 1948 among twenty-three bulbar cases. We are definitely of the opinion that our six survivors in 1949 lived because of the tracheotomy, and without it would surely have died.

But it will take many more reports of the type cited in this editorial before the issue of tracheotomy can be conclusively determined. In the meantime, it would seem reasonable to accept as having been demonstrated that fatalities in bulbar poliomyelitis can be reduced whether or not tracheotomy is the method employed. In either case expert attendants are essential. The establishment of strategically located centers equipped with trained personnel and adequate facilities in all areas where poliomyelitis is epidemic would seem to be a desirable goal.

The report on the First International Poliomyelitis Conference published by J. B. Lippincott Company is highly recommended to those interested.

L. F. H.

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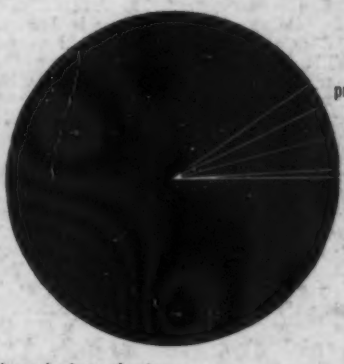

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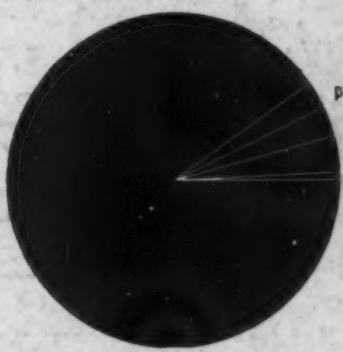
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